Official Title: A Phase III, Randomized, Double-Blinded, Placebo-Controlled Study of Tiragolumab, an Anti-Tigit Antibody, in Combination with Atezolizumab Compared with Placebo in Combination with Atezolizumab in Patients with Previously Untreated Locally Advanced Unresectable or Metastatic PD-L1-Selected Non-Small Cell Lung Cancer

NCT Number: NCT04294810

Document Date: Protocol Amendment Version 7: 14-Nov-2023

PROTOCOL

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED STUDY OF TIRAGOLUMAB, AN ANTI-TIGIT ANTIBODY, IN COMBINATION WITH ATEZOLIZUMAB COMPARED WITH PLACEBO IN COMBINATION WITH ATEZOLIZUMAB IN PATIENTS WITH PREVIOUSLY UNTREATED LOCALLY ADVANCED UNRESECTABLE OR METASTATIC PD-L1–SELECTED NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO41717
VERSION NUMBER:	7
TEST PRODUCTS:	Tiragolumab (RO7092284) Atezolizumab (RO5541267)
STUDY PHASE	Phase III
REGULATORY AGENCY IDENTIFIERS:	IND Number: 129258 EudraCT Number: 2019-002925-31 EU CT Number: 2022-502482-17-00 CIV ID: CIV-23-01-042092, CIV-23-01-042146, CIV-23-01-042093 NCT Number: NCT04294810
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

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PROTOCOL HISTORY

Protocol		Associated Country- or Region-Specific Protocols		
Version	**Date Final**	**Country or Region**	**Version**	**Date Final**
7	See electronic date stamp on the final page of this document.	China	7	See electronic date stamp on the final page of China document.
6	2 June 2023	China	6	2 June 2023
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4	3 November 2021	China	4	10 December 2021
3	2 November 2020	China	3	9 June 2021
2	8 May 2020	China	2	27 July 2020
1	30 September 2019	VHP	1	27 March 2020

PROTOCOL AMENDMENT, VERSION 7:
RATIONALE

Protocol GO41717 has been amended primarily to update safety language to align with the Atezolizumab Investigator's Brochure, Version 20. Substantive changes to the protocol, along with a rationale for each change, are summarized below:

- The list of approved indications for atezolizumab has been updated to include alveolar soft part sarcoma (Section 1.7).
- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 5.7).
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 20 (Appendix 10).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED STUDY OF TIRAGOLUMAB, AN ANTI-TIGIT ANTIBODY, IN COMBINATION WITH ATEZOLIZUMAB COMPARED WITH PLACEBO IN COMBINATION WITH ATEZOLIZUMAB IN PATIENTS WITH PREVIOUSLY UNTREATED LOCALLY ADVANCED UNRESECTABLE OR METASTATIC PD-L1–SELECTED NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO41717
VERSION NUMBER:	7
TEST PRODUCTS:	Tiragolumab (RO7092284) Atezolizumab (RO5541267)
SPONSOR NAME:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form to the Sponsor or its designee.

PROTOCOL SYNOPSIS

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED STUDY OF TIRAGOLUMAB, AN ANTI-TIGIT ANTIBODY, IN COMBINATION WITH ATEZOLIZUMAB COMPARED WITH PLACEBO IN COMBINATION WITH ATEZOLIZUMAB IN PATIENTS WITH PREVIOUSLY UNTREATED LOCALLY ADVANCED UNRESECTABLE OR METASTATIC PD-L1–SELECTED NON–SMALL CELL LUNG CANCER**
REGULATORY AGENCY IDENTIFIERS:	IND Number: 129258 EudraCT Number: 2019-002925-31 EU CT Number: 2022-502482-17-00 CIV ID: CIV-23-01-042092, CIV-23-01-042146, CIV-23-01-042093 NCT Number: NCT04294810

STUDY RATIONALE

This study will evaluate the efficacy and safety of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated locally advanced, unresectable or metastatic PD-L1–selected non–small cell lung cancer (NSCLC), with no epidermal growth factor receptor (*EGFR)* mutation or anaplastic lymphoma kinase (*ALK*) translocation.

The study population is selected on the basis of a high tumor tissue PD-L1 expression, as assessed by central testing, defined by meeting at least one of the following thresholds specific to each assay: PD-L1 immunohistochemistry (IHC) 22C3 pharmDx assay (tumor proportion score [TPS] ≥ 50%), VENTANA PD-L1 (SP142) Assay (tumor cells ≥ 50% [TC3] or immune cells ≥ 10% [IC3]), or investigational VENTANA PD-L1 (SP263) companion diagnostic (CDx) Assay (tumor cells ≥ 50%).

OBJECTIVES AND ENDPOINTS

Primary Objective	Corresponding Endpoint
• The primary efficacy objective for this study is to evaluate the efficacy of tiragolumab plus atezolizumab compared with placebo plus atezolizumab on the basis of the following co-primary endpoints in the primary analysis set	• PFS after randomization, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first • OS, defined as the time from randomization to death from any cause
• The safety objective for this study is to evaluate the safety and tolerability of tiragolumab plus atezolizumab compared with placebo plus atezolizumab on the basis of the following endpoints	• Incidence and severity of adverse events, with severity determined according to the NCI CTCAE v5.0 • Severity for CRS will also be determined according to the ASTCT CRS consensus grading scale

Secondary Objectives	Corresponding Endpoints
• The secondary efficacy objective for this study is to evaluate the efficacy of tiragolumab plus atezolizumab compared with placebo plus atezolizumab on the basis of the following endpoints	• Investigator-assessed PFS according to RECIST v1.1 and OS in the SAS • Confirmed ORR, defined as the proportion of patients with a confirmed objective response (i.e., CR or PR on two consecutive occasions ≥4 weeks apart), as determined by the investigator according to RECIST v1.1 • DOR for patients with confirmed ORR, defined as the time from the first occurrence of a documented confirmed objective response to disease progression as determined by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first • PFS rate at 6 months and 12 months, defined as the proportion of patients who have not experienced disease progression as determined by the investigator according to RECIST v1.1 or death from any cause at 6 months and at 12 months, respectively • OS rate at 12 months and 24 months, defined as the proportion of patients who have not experienced death from any cause at 12 and 24 months, respectively • TTCD in patient-reported physical functioning and GHS/QoL, as measured by the EORTC QLQ-C30

ASTCT = American Society for Transplantation and Cellular Therapy; CR = complete response; CRS = cytokine-release syndrome; DOR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; GHS = global health status; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; QoL = quality of life; QLQ-C30 = Quality of Life-Core 30 Questionnaire; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SAS = secondary analysis set; TTCD = time to confirmed deterioration.

OVERALL DESIGN AND STUDY POPULATION

This is a Phase III, randomized, double-blinded, placebo-controlled, global, multicenter study designed to evaluate the efficacy and safety, of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated locally advanced, unresectable or metastatic PD-L1–selected NSCLC.

Several key aspects of the study design and study population are summarized below.

Phase:	Phase III	**Population Type:**	Adult patients
Control Method:	Placebo	**Population Diagnosis or Condition:**	Previously untreated, locally advanced unresectable or metastatic non-small cell lung cancer that is PD-L1 selective
Interventional Model:	Parallel group	**Population Age:**	≥18 years
Test Products:	Tiragolumab (RO7092284)	**Site Distribution:**	Multisite and multiregional

	Atezolizumab (RO5541267)		
Active Comparator:	Not Applicable	**Study Intervention Assignment Method:**	Randomization
Number of Arms:	Two	**Number of Participants to Be Enrolled:**	Approximately 560 patients

STUDY TREATMENT

In the experimental arm, patients will receive atezolizumab at a fixed dose of 1200 mg administered by IV infusion every 3 weeks (Q3W) on Day 1 of each 21-day cycle, followed by tiragolumab at a fixed dose of 600 mg administered to patients by IV infusion Q3W on Day 1 of each 21-day cycle.

In the control arm, patients will receive atezolizumab at a fixed dose of 1200 mg administered by IV infusion Q3W on Day 1 of each 21-day cycle, followed by placebo administered by IV infusion Q3W on Day 1 of each 21-day cycle.

There will be no dose modifications, including dose reductions, for tiragolumab/placebo or atezolizumab in this study; however, the dosing of atezolizumab and/or tiragolumab may be delayed due to drug-related toxicity, at the discretion of the investigator.

DURATION OF PARTICIPATION

The total duration of study participation for each individual is expected to be approximately 59 months.

COMMITTEES

Independent Committees:	Steering Committee Independent Data Monitoring Committee

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
1 L (treatment)	first-line (treatment)
2 L (treatment}	second-line (treatment)
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ALK	anaplastic lymphoma kinase (gene)
ASTCT	American Society for Transplantation and Cellular Therapy
$CD4^+$	cluster of differentiation 4
$CD8^+$	cluster of differentiation 8
CDx	companion diagnostic
CHO	Chinese hamster ovary
CIT	cancer immunotherapy
COVID-19	coronavirus disease 2019
CR	complete response
CRS	cytokine-release syndrome
CT	computed tomography (scan)
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DOR	duration of response
EAE	experimental autoimmune encephalitis
EBUS	endobronchial ultrasound
EBV	Epstein-Barr virus
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor (gene)
EORTC	European Organisation for Research and Treatment of Cancer
EUS	endoscopic ultrasound
EUS-FNA	endoscopic ultrasound-guided fine-needle aspiration
Fc	fragment crystallizable
GHS	global health status
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus

Abbreviation	Definition
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
HRQoL	health-related quality of life
IC	immune cell
ICH	International Council for Harmonization
iDMC	independent Data Monitoring Committee
IFN	interferon
IgG1/κ	immunoglobulin G1 kappa
IgM	immunoglobulin M
IHC	immunohistochemistry
IL-2	interleukin-2
IL-10	interleukin-10
IL46	Item List 46 (question)
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRF	Independent Review Facility
IRR	infusion-related reaction
ITT	intent-to-treat (population)
IxRS	interactive voice or web-based response system
KRAS	Kirsten rat sarcoma viral oncogene homolog (gene)
MAb	monoclonal antibody
MAS	macrophage activation syndrome
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	next-generation sequencing
NK	natural killer (cell)
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PAS	primary analysis set
PCR	polymerase chain reaction
PD	pharmacodynamic

Abbreviation	Definition
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
[redacted]	
PVR	poliovirus receptor
QLQ-C30	Quality of Life Questionnaire for Cancer
QoL	quality of life
Q3W	every 3 weeks
RBR	Research Biosample Repository
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	secondary analysis set
TC	tumor cell
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TNF-α	tumor necrosis factor-α
TPS	tumor proportion score
TTCD	time to confirmed deterioration
ULN	upper limit of normal
VAS	visual analog scale
VCA	viral capsid antigen
WES	whole exome sequencing
WGS	whole genome sequencing
WT	wild type

1. BACKGROUND

1.1 BACKGROUND ON LUNG CANCER

Lung cancer remains the leading cause of cancer deaths worldwide, accounting for approximately 12% of all new cancers in 2018 (Bray et al. 2018). In 2019 in the United States, it was estimated that there were 228,150 new cases of lung cancer (116,440 in men and 111,710 in women) and 142,670 lung cancer deaths (American Cancer Society 2019). Similar data from Europe estimate that in 2018 there were 387,900 lung cancer deaths (267,300 in men and 120,600 in women) (Ferlay et al. 2019).

Non–small cell lung cancer (NSCLC) is the predominant subtype, accounting for approximately 85% of all cases (Molina et al. 2008; Howlader et al. 2014). Non–small cell lung cancer can be divided into two major histologic types: adenocarcinoma and squamous cell carcinoma (Travis et al. 2011). Adenocarcinoma histology accounts for more than half of all NSCLC, while squamous cell histology accounts for approximately 25% of NSCLC (Langer et al. 2010). The remaining cases of NSCLC are represented by large-cell carcinoma, neuroendocrine tumors, sarcomatoid carcinoma, and poorly differentiated histology.

The overall 5-year survival rate for advanced disease treated with chemotherapy remains poor, depending on geographic location (Cetin et al. 2011). Poor prognostic factors for survival in patients with NSCLC include advanced stage of disease at the time of initial diagnosis, poor performance status, and a history of unintentional weight loss. More than half of the patients with NSCLC are diagnosed with distant disease, which directly contributes to poor survival prospects.

There are recognized differences in disease characteristics between adenocarcinoma and squamous NSCLC. Non-squamous tumors are more commonly located in the lung parenchyma distal to the central airways, whereas squamous tumors commonly present in the central airways and typically remain localized in the bronchial epithelium (Hirsch et al. 2008). Evaluation of NSCLC tumor tissue reveals cytologic differences between adenocarcinoma (characterized by glandular architecture) and the squamous cell type (characterized by keratinization, intracellular bridges, and central necrosis). In cases where the tumor sample is poorly differentiated or there is limited tissue available, immunohistochemical biomarkers may support the histologic diagnosis. Thyroid transcription factor−1 is strongly expressed in adenocarcinoma and infrequently expressed in squamous cells. In contrast, p63, CK5/6, and 34-E12 are strongly expressed in squamous cell carcinoma and are less frequently expressed in adenocarcinoma (Travis et al. 2011).

Genetic changes that have prognostic and/or predictive significance in NSCLC include mutations in the epidermal growth factor receptor (*EGFR*) gene, rearrangements in the anaplastic lymphoma kinase (*ALK*) gene, and mutations in the Kirsten rat sarcoma viral

oncogene homolog (*KRAS*) gene. The rates of these mutations differ between adenocarcinoma and squamous cell carcinoma. For example, *EGFR* kinase domain mutations have been reported in 10%–40% of patients with adenocarcinoma NSCLC but are infrequently observed in patients with squamous NSCLC (Herbst et al. 2008). The *ALK* fusion oncogene, recognized as a driver of lung tumorigenesis, is observed in approximately 7% of patients with adenocarcinoma but is rare in squamous histology (Herbst et al. 2008; Langer et al. 2010). In addition, *KRAS* mutations can be observed in up to 30% of adenocarcinoma NSCLC, while they are rare in squamous NSCLC (Travis et al. 2011).

1.2 FIRST-LINE TREATMENT FOR NON–SMALL CELL LUNG CANCER WITHOUT AN *EGFR* MUTATION OR *ALK* REARRANGEMENT

1.2.1 First-Line Chemotherapy for Advanced NSCLC

Patients with previously untreated NSCLC that does not harbor an activating *EGFR* mutation or *ALK* gene rearrangement have been typically treated with platinum-based chemotherapy. The standard-of-care chemotherapy in the first-line (1 L) setting often involves either cisplatin or carboplatin and a taxane or pemetrexed, with or without bevacizumab for non-squamous NSCLC, and cisplatin or carboplatin and gemcitabine for squamous NSCLC. However, the benefit conferred by platinum-based doublets appears to have reached a plateau in objective response rate (ORR; approximately 15%–22%) and median survival (7–10 months). The addition of bevacizumab to carboplatin and paclitaxel in the treatment of non-squamous NSCLC resulted in an increase in response rate from 15% to 35% and an increase in median overall survival (OS) from 10 to 12 months.

1.2.2 First-Line Immunotherapy Plus Chemotherapy for Advanced NSCLC in an All-Comer Population Irrespective of PD-L1 Expression

Immune checkpoint inhibitors, including programmed death–ligand 1/programmed death–1 (PD-L1/PD-1)–blocking antibodies, have emerged as a new therapeutic option for the 1 L treatment of metastatic NSCLC. In the randomized Phase III Impower150 (GO29436) study, OS and progression-free survival (PFS) were significantly prolonged with atezolizumab, bevacizumab, paclitaxel, and carboplatin relative to bevacizumab, paclitaxel, and carboplatin in patients with advanced non-squamous NSCLC without an activating *EGFR* mutation or *ALK* gene rearrangement (OS hazard ratio [HR] = 0.78; p = 0.02; median OS: 19.2 vs. 14.7 months; PFS HR = 0.62; p < 0.001; median PFS: 8.3 vs. 6.8 months; Socinski et al. 2018).

In the KEYNOTE-189 study, OS and PFS were also significantly improved with pembrolizumab, pemetrexed, and carboplatin relative to pemetrexed and carboplatin in patients with advanced non-squamous NSCLC (OS HR = 0.56, p < 0.00001, median OS 22.0 vs. 10.7 months; PFS HR = 0.52, p < 0.001, median PFS: 8.8 vs. 4.9 months

(Gandhi et al. 2018; Gadgeel et al. 2019). Results from these studies have led to the approval in the United States and other countries of atezolizumab and pembrolizumab with the corresponding chemotherapy regimens as 1 L therapy for patients with advanced non-squamous NSCLC without an activating *EGFR* mutation or *ALK* gene rearrangement, irrespective of PD-L1 expression. In addition, based on the KEYNOTE-407 study, the combination of pembrolizumab with paclitaxel or nab-paclitaxel and carboplatin is approved for the 1 L treatment of advanced squamous NSCLC (Paz-Ares et al. 2018).

1.2.3 First-Line Immunotherapy as Monotherapy for Advanced NSCLC with PD-L1 Expression

Chemotherapy-based regimens are associated with substantial toxicities and are generally poorly tolerated by elderly patients and by patients with poor performance status. Therefore, novel therapies that deliver an improved therapeutic index are needed for NSCLC. Pursuing personalized cancer immunotherapy (CIT), several Phase III trials have been conducted to investigate chemotherapy-free regimens involving anti–PD-L1/PD-1 inhibitors versus standard cytotoxic chemotherapy in treatment-naive patients with PD-L1–positive NSCLC without an activating *EGFR* mutation or *ALK* gene rearrangement.

The KEYNOTE-024 study demonstrated significant improvement in survival with pembrolizumab monotherapy over standard platinum-based doublets in advanced NSCLC with high PD–L1 expression (tumor proportion score [TPS] $\geq$ 50% assessed using the PD-L1 immunohistochemistry [IHC] 22C3 pharmDx assay), with OS HR = 0.63 (95% CI: 0.44% to 0.91%), p = 0.002, median OS 30.0 versus 14.2 months; and PFS HR = 0.50, p < 0.001, median PFS 10.3 versus 6.0 months (Reck et al. 2016, 2019). In the KEYNOTE-042 study in which patients with a TPS $\geq$ 1% (determined using the PD-L1 IHC 22C3 pharmDx assay) were enrolled, survival outcomes of pembrolizumab compared with chemotherapy doublets in the two primary patient populations with a TPS $\geq$ 50% and a TPS $\geq$ 1% were OS HR = 0.69, p = 0.0003, median OS: 20.0 versus 12.2 months, and OS HR = 0.81, p = 0.0018, median OS: 16.7 versus 12.1 months, respectively. However, patients in a prespecified exploratory subgroup with TPS 1%–49% appeared to have similar OS in the two arms: HR = 0.92, median OS 13.4 versus 12.1 months; 95% CI: 0.77 to 1.11 months (Mok et al. 2019). Based on results from these studies, pembrolizumab is approved for the 1 L treatment of patients with metastatic NSCLC without an activating *EGFR* mutation or *ALK* gene rearrangement, whose tumors express PD-L1 (TPS $\geq$ 1%) in the United States and in patients whose tumors express high PD-L1 (TPS $\geq$ 50%) in the European Union.

Recently, atezolizumab monotherapy has also demonstrated a statistically significant and clinically meaningful improvement in OS compared with platinum-based doublet chemotherapy as 1 L treatment of metastatic NSCLC that expresses high PD-L1 in Study GO29431 (IMpower110; Spigel et al. 2019). IMpower110 is a Phase III,

randomized, open-label study evaluating the efficacy and safety of atezolizumab monotherapy compared with platinum-based doublet chemotherapy in PD-L1–selected, chemotherapy-naive patients with advanced non-squamous or squamous NSCLC without *EGFR* or *ALK* mutations (wild type [WT]). Only patients whose tumors expressed PD-L1 (defined as tumor cell [TC]1/2/3 or immune cell [IC]1/2/3, as determined by the VENTANA® [SP142] IHC Assay) were eligible. A total of 572 patients were enrolled and were randomized in a 1:1 ratio to receive atezolizumab monotherapy, cisplatin, or carboplatin (per investigator discretion) combined with either pemetrexed (non-squamous) or gemcitabine (squamous), followed by maintenance therapy with pemetrexed alone (non-squamous) or best supportive care (squamous). The study enrolled patients with an *EGFR* mutation or *ALK* translocation who had disease progression or intolerable toxicity to treatment with a tyrosine kinase inhibitor; these patients were excluded from the analysis population, which included WT patients only (554 WT patients). The primary efficacy endpoint was OS by PD-L1 subgroup (TC3/IC3-WT; TC2/3 IC2/3-WT; and TC1/2/3 IC1/2/3-WT), as determined using the VENTANA PD-L1 (SP142) IHC Assay. Key secondary endpoints included investigator-assessed PFS, ORR, and duration of response (DOR).

At the time of the interim OS analysis (clinical cutoff date: 10 September 2018), atezolizumab monotherapy showed a statistically significant and clinically meaningful improvement in OS compared with chemotherapy in patients with high PD-L1 expression (TC3/IC3-WT) with a stratified HR (95% CI) of 0.595 (0.398 to 0.890), $p=0.0106$, median OS 20.2 months versus 13.1 months (see Table 1). Because the OS statistical testing boundary was not crossed in the TC2/3 or IC2/3-WT or TC1/2/3 or IC1/2/3-WT subgroups at this interim analysis, the study will continue to the OS final analysis for these subgroups.

As shown in Table 1, the study also demonstrated a clinically meaningful improvement in investigator-assessed PFS for atezolizumab in patients with high PD-L1 expression (TC3/IC3-WT) with a stratified HR (95% CI) of 0.630 (0.449 to 0.884) and median PFS of 8.1 months versus 5.0 months. Atezolizumab monotherapy was also associated with improved ORR in the TC3/IC3-WT subgroup, with durable responses compared to chemotherapy. Based on the results from this study, atezolizumab monotherapy is approved in the European Union and United States, for the 1 L treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression (TC3 or IC3, with TC3 defined as PD-L1 staining on ≥50% of TC and IC3, defined as PD-L1 staining ≥ 10% on IC) with no EGFR or ALK genomic tumor aberrations.

Table 1 IMpower110 Key Primary and Secondary Efficacy Endpoints

	TC3 or IC3-WT		TC2/3 or IC2/3-WT		TC1/2/3 or IC1/2/3-WT	
Treatment	**Chemo (n=98)**	**Atezo (n=107)**	**Chemo (n=162)**	**Atezo (n=166)**	**Chemo (n=277)**	**Atezo (n=277)**
OS						
Median (mos)	13.1	20.2 (+7.1)	14.9	18.2 (+3.3)	14.1	17.5 (+3.4)
Stratified HR (95% CI)	0.595 (0.398 to 0.890)		0.717 (0.520 to 0.989)		0.832 (0.649 to 1.067)	
Stratified log-rank p-value	0.0106		0.0416		0.1481 [a]	
PFS						
Median (mos)	5.0	8.1 (+3.1)	5.5	7.2 (+1.7)	5.5	5.7 (+0.2)
Stratified HR (95% CI)	0.630 (0.449 to 0.884)		0.672 (0.517 to 0.875)		0.772 (0.633 to 0.941)	
Stratified log-rank p-value	0.0070 [a]		0.0030 [a]		0.0104 [a]	
ORR						
Confirmed ORR (95% CI)	28.6% (19.90 to 38.58)	38.3% (29.08 to 48.22)	32.1% (24.99 to 39.88)	30.7% (23.81 to 38.34)	31.8% (26.33 to 37.61)	29.2% (23.95 to 34.98)
DOR						
Responders [b]	28	41	88	81	88	81
Median (mos) (95% CI)	6.7 (5.5 to 17.3)	NE (11.8 to NE)	5.8 (5.1 to 9.9)	NE (11.8 to NE)	5.7 (4.8 to 9.7)	NE (11.8 to NE)

Atezo = atezolizumab; chemo = chemotherapy; CI = confidence interval; CR = complete response; DOR = duration of response; HR = hazard ratio; IC = immune cell; mos = months; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; TC = tumor cell; WT = wild type.

[a] Included for descriptive purposes only.

[b] Responders are the number of patients with a CR or a PR.

Overall, chemotherapy-free options with 1 L immunotherapy offer patients with advanced NSCLC expressing PD-L1 significant survival benefits as well as a more tolerable toxicity profile. Despite improvements and benefits with PD-L1/PD-1–targeting agents, nearly all patients experience disease progression. Consequently, new molecules and combinations, including novel immunotherapy combinations, are needed to address this unmet medical need.

1.3 TIGIT PATHWAY IN CANCER AS A POTENTIAL ANTI-CANCER THERAPY

T-cell immunoreceptor with Ig and ITIM domains (TIGIT) is a novel immune inhibitory receptor that is a member of the Ig super family (Yu et al. 2009; Manieri et al. 2017). TIGIT is expressed on the surface of activated T-cell and natural killer (NK)-cell subsets and interacts with high affinity with CD155 (also known as the poliovirus receptor [PVR]; Yu et al. 2009). Genetic ablation of TIGIT in T cells in mice results in exacerbated T-cell responses in nonclinical models of autoimmune and viral infections, demonstrating the role of TIGIT in inhibiting T-cell responses (Joller et al. 2011; Johnston et al. 2014). TIGIT expression is elevated in the tumor microenvironment in many human tumors, is coordinately expressed with other checkpoint immune receptors such as PD-1 and is associated with impaired T-cell function and anti-tumor immunity (Johnston et al. 2014). Activation of TIGIT on T cells and NK cells limits cellular proliferation, effector cytokine production, and killing of target TCs (Stanietsky et al. 2009; Yu et al. 2009; Johnston et al. 2014; Wang et al. 2015; Manieri et al. 2017).

TIGIT is expressed in a wide variety of human tumors, including NSCLC, and is highly correlated with T-cell infiltration and PD-1 expression (Johnston et al. 2014). Fluorescence-activated cell sorting analysis of fresh tumor samples showed that TIGIT and PD-1 are also co-expressed on tumor-infiltrating T cells. TIGIT expression ranges from 30% to 80% and from 50% to 80% on tumor-infiltrating cluster of differentiation 4 ($CD4^+$) and cluster of differentiation 8 ($CD8^+$) T cells, respectively (Johnston et al. 2014). It has also been reported that tumor-infiltrating lymphocytes from early-stage primary NSCLCs co-express TIGIT with PD-1, suggesting that TIGIT expression may be important throughout the development of NSCLC (Tassi et al. 2017).

Therefore, TIGIT is a potential target for therapeutic intervention aimed at restoring the immune response against the tumor, especially in NSCLC. Agents that inhibit the activity of TIGIT may relieve an important source of tumor-associated immune suppression and may enhance the activity of other immune-based therapies, such as atezolizumab, an inhibitor of PD-L1. Early nonclinical results using genetically deficient mice and blocking antibodies reveal a key role for TIGIT in regulating T-cell responses. Together these data support the hypothesis that anti-TIGIT in combination with anti–PD-L1 may reactivate anti-tumor immunity in NSCLC to provide clinical benefit to patients.

1.4 PD-L1/PD-1 PATHWAY IN CANCER

PD-L1 is a cell surface protein that is broadly expressed TCs and tumor-infiltrating ICs in many human cancers, including lung cancer. PD-L1 binds to PD-1 and B7.1, two known inhibitory receptors whose expression on activated T-cells is sustained in states of chronic stimulation such as chronic infection or cancer (Blank et al. 2005; Keir et al. 2008). Ligation of PD-L1 with PD-1 or B7.1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to a functional inactivation or inhibition of

T-cells. Aberrant expression of PD-L1 on TCs has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1/PD-1 and PD-L1/B7.1 pathways represents an attractive strategy to reinvigorate tumor-specific T-cell immunity.

Inhibitors of PD-L1 and PD-1 have demonstrated clinical efficacy in a wide range of tumor types, including NSCLC. The evidenced benefit has led to approvals of anti–PD-L1/PD-1 antibodies (such as atezolizumab, pembrolizumab, and nivolumab) for the treatment of metastatic NSCLC. Nevertheless, many patients with NSCLC treated with PD-L1/PD-1 blockade alone do not experience sustained clinical benefit, underscoring the need to explore CIT combinations with the potential to overcome intrinsic or acquired resistance to checkpoint inhibition. Antagonists that target additional inhibitory receptors have the potential to enhance such anti-tumor T-cell responses. Hence, such co-inhibitory antagonists have emerged as attractive combination partners for anti–PD-L1/PD-1 on the basis of their complementary mechanism of action.

1.5 COMBINED INHIBITION OF THE TIGIT AND PD-L1/PD-1 PATHWAYS AS POTENTIAL ANTI-CANCER THERAPY

The inhibitory immunoreceptor TIGIT has been shown to limit the effector function of tumor-associated lymphocytes. Activation of TIGIT on T cells and NK cells limits proliferation, effector cytokine production, and killing of target TCs. Therefore, in the context of the tumor microenvironment, TIGIT acts to limit anti-tumor immune responses. Interference with TIGIT–PVR interaction may enhance the magnitude and quality of the tumor-specific T-cell responses through increased expansion of T cells as well as improved T-cell priming and/or effector function. Because TIGIT and PD-1 are coordinately expressed by infiltrating T cells in several human tumors, inhibition of the TIGIT/PVR pathway may complement and potentiate the anti-tumor activity of a PD-L1 pathway inhibitor such as atezolizumab.

In preclinical models, concomitant blockade of both TIGIT and PD-L1/PD-1 pathways demonstrated superior efficacy over the respective single-agent treatments. In one such preclinical model, tumor-infiltrating T cells demonstrate increased interferon (IFN)-γ expression (a hallmark of activation and anti-tumor activity of T cells) only when both TIGIT and PD-1 are blocked concurrently and not when each individual pathway is blocked by the respective single-agent treatment. Notably, co-inhibition of TIGIT and PD-L1 in this syngeneic tumor model was not associated with loss of body weight or any other observable adverse responses. On the basis of these studies, it is hypothesized that the combination of anti-TIGIT with anti–PD-L1/PD-1 may result in activation of anti-tumor immune responses leading to enhanced killing of TCs and improved clinical responses in patients with metastatic NSCLC than with either agent alone.

This hypothesis led to Study GO40290, a global Phase II, randomized, double-blinded, placebo-controlled, multicenter study, designed to evaluate the safety and efficacy of

tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated locally advanced, unresectable or metastatic PD-L1–selected NSCLC (see Section 1.6.2).

1.6 BACKGROUND ON TIRAGOLUMAB

Tiragolumab (formerly, MTIG7192A) is a fully human immunoglobulin G1 kappa (IgG1/κ) monoclonal antibody (mAb) derived in open monoclonal technology rats that binds to TIGIT and prevents its interaction with PVR. The recombinant antibody is produced in Chinese hamster ovary (CHO) cells and consists of two heavy chains (456 amino acid residues each) and two light chains (220 amino acid residues each). [redacted] The predicted molecular weight of tiragolumab is 148,409 Da (peptide chains only, without heavy chain C terminal lysine residue).

Therapeutic blockade of TIGIT by means of tiragolumab represents an attractive strategy for cancer therapy and is expected to enhance the magnitude and quality of the tumor-specific T-cell responses, which may result in improved meaningful anti-tumor activity when tiragolumab is used as a single agent or in combination with other CITs.

Tiragolumab is being investigated in clinical studies as a potential therapy against various tumor types.

Refer to the Tiragolumab Investigator's Brochure for additional details on the nonclinical and clinical studies for tiragolumab.

1.6.1 Nonclinical Data with Tiragolumab

The nonclinical strategy for tiragolumab was to demonstrate in vitro and in vivo pharmacology, to evaluate the pharmacokinetic (PK) profile, to demonstrate an acceptable safety profile, and to identify a Phase Ia and Phase Ib starting dose for tiragolumab. Comprehensive pharmacology, PK, and toxicology evaluations were thus undertaken with tiragolumab.

The completed nonclinical pharmacology studies demonstrate that tiragolumab binds to TIGIT and prevents TIGIT–PVR interactions. Tiragolumab is a human IgG1 mAb and therefore binds to Fcγ receptors and is capable of mediating antibody-dependent cell-mediated cytotoxicity (ADCC). However, neither complement-dependent cytotoxicity nor increased cytokine release was detected in the nonclinical models following tiragolumab treatment compared with the control-treated models. In the CT26 syngeneic colon tumor model, co-inhibition of the TIGIT/PVR and PD-L1/PD-1 pathways improve anti-tumor activity compared with inhibition of only one pathway with either monotherapy in the absence of loss of body weight or any other observable adverse responses. Taken together, the data provide a rationale for evaluating the combination of anti-TIGIT with anti–PD-L1 agents in clinical studies.

Because tiragolumab does not cross-react with rodent TIGIT, the pharmacokinetics and toxicokinetics of tiragolumab were investigated in cynomolgus monkeys. Overall, the nonclinical PK behavior observed for tiragolumab is consistent with that expected for a receptor-targeting human IgG1 mAb. [redacted]

Overall, the nonclinical pharmacokinetics and toxicokinetics observed for tiragolumab supported entry into clinical studies, including providing adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of down modulating the PD-L1/PD-1 pathway and supported entry into clinical studies.

Refer to the Tiragolumab Investigator's Brochure for additional details on nonclinical studies.

1.6.2 Clinical Experience with Tiragolumab

Refer to the Tiragolumab Investigator's Brochure for details on all clinical studies conducted to date.

1.6.2.1 Ongoing Clinical Studies with Tiragolumab

Tiragolumab has been tested in a Phase I study (GO30103), a first-in-human, combined Phase Ia/Phase Ib, open-label, dose-escalation, multicenter study. The study evaluated the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of tiragolumab administered as a single agent by IV infusion every 21 days (Phase Ia) or in combination with atezolizumab at 1200 mg administered by IV infusion every 21 days (Phase Ib) to patients with locally advanced or metastatic malignancies. The most common cancer types of patients enrolled in the study include NSCLC, head and neck squamous cell carcinoma, urinary bladder cancer, and renal cell cancer. Refer to the Tiragolumab Investigator's Brochure for further details.

The combination of tiragolumab plus atezolizumab was further evaluated in patients with NSCLC in Study GO40290, a global Phase II, randomized, double-blinded, placebo-controlled study. This study was designed to evaluate the combination of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated, locally advanced, unresectable or metastatic PD-L1–selected NSCLC (TPS $\geq$ 1%).

Safety data for single-agent tiragolumab from the Phase I study GO30103, and safety and efficacy data for the combination of tiragolumab and atezolizumab from the Phase II study GO40290 are summarized below.

1.6.2.2 Clinical Safety of Tiragolumab

In the Phase I study (GO30103), as of 3 December 2018, tiragolumab had been administered to 182 safety-evaluable patients in both the Phase Ia and Phase Ib portions of the study. Refer to the Tiragolumab Investigator's Brochure for further details and the most current information.

[redacted]

[redacted]

Clinical Safety of Single-Agent Tiragolumab: Study GO30103

In Study GO30103, as of 3 December 2018, 42 patients had been enrolled in the Phase Ia portion. Refer to the Tiragolumab Investigator's Brochure for further details and the most current information on the adverse events observed in patients treated with single-agent tiragolumab in Study GO30103.

Clinical Safety of Tiragolumab Plus Atezolizumab: Study GO30103

In Study GO30103, as of 3 December 2018, 163 patients had been enrolled in the Phase Ib portion, including 23 patients who crossed over from the Phase Ia portion following disease progression.

Refer to the Tiragolumab Investigator's Brochure for further details and the most current information on the adverse events observed in patients treated with tiragolumab and atezolizumab across various tumor types in the Phase Ib portion of Study GO30103.

Clinical Safety of Tiragolumab Plus Atezolizumab in Patients with NSCLC: Study GO40290

In the Phase II, randomized, double-blinded GO40290 study, as of 30 June 2019, a total of 135 patients had been enrolled. A total of 67 patients were administered tiragolumab (600 mg) in combination with atezolizumab (1200 mg) every 3 weeks (Q3W), and 68 patients were administered placebo in combination with atezolizumab Q3W.
The safety profile was comparable between the tiragolumab plus atezolizumab arm and the placebo plus atezolizumab arm for all grade adverse events (98.5% vs. 95.6%), Grade $\geq$3 adverse events (41.8% vs. 44.1%), Grade 5 adverse events (3.0% vs. 7.4%), serious adverse events (34.3% vs. 35.3%), and adverse events leading to study treatment withdrawal (7.5% vs. 10.3%). Study treatment–related adverse events

occurred at a higher frequency in the tiragolumab plus atezolizumab arm (80.6%) compared with that in the placebo plus atezolizumab arm (72.1%).

Adverse events that occurred at a higher frequency (≥5% difference between arms) in the tiragolumab plus atezolizumab arm were infusion-related reactions (IRRs; 28.4% vs. 10.3%), fatigue (22.4% vs. 13.2%), pruritus (19.4% vs. 11.8%), rash (19.4% vs. 8.8%), arthralgia (16.4% vs. 8.8%), peripheral edema (10.4% vs. 4.4%), maculopapular rash (9.0% vs. 2.9%), pleural effusion (9.0% vs. 2.9%), and back pain (9.0% vs. 2.9%). Adverse events that occurred at a higher frequency in the placebo plus atezolizumab arm included dyspnea (13.4% vs. 20.6%), productive cough (4.5% vs. 10.3%), increased ALT (4.5% vs. 10.3%), respiratory tract infection (3.0% vs. 8.8%), hypercalcemia (0% vs. 5.9%). Grade ≥3 adverse events (with a ≥2% difference between arms) that occurred at a higher frequency in the tiragolumab plus atezolizumab arm were pneumonia (9.0% vs. 4.4%), pleural effusion (6.0% vs.1.5%), increased lipase (6.0% vs. 2.9%), hypokalemia (3.0% vs. 0%); Grade ≥3 adverse events that occurred at a higher frequency in the placebo plus atezolizumab arm were pulmonary embolism (0% vs. 2.9%), increased amylase (0% vs. 2.9%), and asthenia (0% vs. 2.9%).

Grade 5 adverse events that occurred in the tiragolumab plus atezolizumab arm were Epstein-Barr virus (EBV) infection and pyrexia (reported for 1 patient each), and Grade 5 adverse events in the placebo plus atezolizumab arm were cardiorespiratory arrest, cerebrovascular accident, multiple organ dysfunction syndrome, pneumonia, and pulmonary embolism (reported for 1 patient each).

Using a comprehensive medical concepts strategy, immune-mediated adverse events were reported with a higher frequency in the tiragolumab plus atezolizumab arm (65.7%) compared with the placebo plus atezolizumab arm (47.1%). The difference ≥10% difference between arms was predominantly attributed to events of immune-mediated rash (preferred terms of rash, maculopapular rash, dermatitis, pruritic rash, eczema, erythema, and folliculitis; 38.8% vs. 14.7%) and IRRs (preferred term of infusion-related reaction; 28.4% vs. 10.3%).

Refer to the Tiragolumab Investigator's Brochure for further details and the most current information on the adverse events observed in patients treated with tiragolumab plus atezolizumab.

1.6.2.3 Clinical Activity of Tiragolumab Plus Atezolizumab

Clinical Activity of Tiragolumab Plus Atezolizumab across Various Tumor Types: Study GO30103

As of the clinical cutoff date of 3 December 2018, tumor response assessment data using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 were available for 42 patients in the Phase Ia portion and 163 patients in Phase Ib portion of the study with advanced cancer in the Phase I study GO30103.

In the Phase Ia, there were no complete responses (CRs) or partial responses (PRs). Best overall response of stable disease, as determined per RECIST v1.1, was observed in 8 of 42 patients [redacted]

Refer to the Tiragolumab Investigator's Brochure for further details and the most current information on the clinical activity in patients treated to date with tiragolumab as a single agent or in combination with atezolizumab across tumor types.

Clinical Activity of Tiragolumab Plus Atezolizumab in Patients with NSCLC: Study GO40290

Study GO40290 is an ongoing, global Phase II, randomized, double-blinded, placebo-controlled study in 1 L NSCLC. The co-primary endpoints were confirmed ORR and investigator-assessed PFS per RECIST v1.1. Secondary endpoints included duration of response (DOR), OS, safety, pharmacokinetics, and immunogenicity.

Patients were eligible if they were ≥18 years old with Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 and had previously untreated, locally advanced unresectable or metastatic PD-L1–selected NSCLC, without a sensitizing *EGFR* mutation or *ALK* rearrangement.

For the purposes of PD-L1 selection, formalin-fixed tumor samples were assessed locally using the commercially available PD-L1 IHC 22C3 pharmDx assays (Dako) [redacted] PD-L1–selected tumors were defined as tumors with a TPS ≥1% using the PD-L1 IHC 22C3 pharmDx assay.

Eligible patients were stratified by the PD-L1 IHC 22C3 pharmDx assay result (TPS 1%–49% vs. TPS ≥50%), tumor histology (non-squamous vs. squamous), and history of tobacco use (yes vs. no).

As of the primary clinical cutoff date of 30 June 2019, a total of 135 patients with a PD-L1 TPS ≥1% were included in the intent-to-treat (ITT) population and were randomly assigned to receive tiragolumab plus atezolizumab (n=67) or placebo plus atezolizumab (n=68). Of the enrolled patients, 43.0% of patients had a TPS ≥50% relative to 57.0% of patients with a TPS 1%–49%, 59.3% had non-squamous histology compared with 40.7% of patients who had squamous histology, and 10.4% of patients were never-smokers versus 89.6% who had smoked. These three stratification factors were well balanced between treatment groups. Demographics were also generally well balanced between treatment groups, with a median age of 68 years in both the tiragolumab plus atezolizumab and placebo plus atezolizumab arms. There were more females (41.8% vs. 29.4%) and more White patients (62.7% vs. 58.8%) in the tiragolumab plus atezolizumab arm compared with the placebo plus atezolizumab arm.

At the primary analysis, in the ITT population, 48% of patients in the tiragolumab plus atezolizumab arm compared with 28% of patients in the placebo plus atezolizumab arm were still receiving study treatment. In the TPS $\geq$50% population, 65.5% of patients in the tiragolumab plus atezolizumab arm relative to 24.1% of patients in the placebo plus atezolizumab arm were still receiving study treatment.

In all randomized patients with TPS $\geq$1%, the confirmed ORR was higher in the tiragolumab plus atezolizumab arm (31.3%) than in the placebo plus atezolizumab arm (16.2%); investigator-assessed PFS was improved in the tiragolumab plus atezolizumab arm compared with the placebo plus atezolizumab arm (stratified HR=0.57; 95% CI: 0.37 to 0.90; median PFS: 5.4 vs. 3.6 months, respectively).

The improvement in ORR and PFS observed with the combination of tiragolumab plus atezolizumab compared with placebo plus atezolizumab appear to be driven by the subgroup of patients with high PD-L1 expression (TPS $\geq$50%). In the subgroup of patients with TPS $\geq$50%, the confirmed ORR was higher in the tiragolumab plus atezolizumab arm (n=29; 55.2% [95% CI: 35.4% to 75.0%]) than in the placebo plus atezolizumab arm (n=29; 17.2% [95% CI: 1.8% to 32.7%]); investigator-assessed PFS was improved in the tiragolumab plus atezolizumab arm relative to the placebo plus atezolizumab arm (unstratified HR=0.33; 95% CI: 0.15 to 0.72; median PFS: not reached vs. 3.9 months, respectively).

1.6.2.4 Clinical Pharmacokinetics and Immunogenicity of Tiragolumab and Atezolizumab

Clinical Pharmacokinetics and Immunogenicity of Tiragolumab

As of 3 December 2018, a preliminary PK analysis had been conducted based on available data (2−1200 mg of tiragolumab Q3W in the Phase Ia portion and 2−1200 mg of tiragolumab in combination with atezolizumab in the Phase Ib portion of Study GO30103) using standard non-compartmental PK methods (refer to the Tiragolumab Investigator's Brochure for details). Overall, tiragolumab exposures increased in an approximately dose-proportional manner when administered to patients both as a single agent and in combination with atezolizumab. Furthermore, the pharmacokinetics of tiragolumab in combination with atezolizumab appeared to be consistent with the pharmacokinetics of tiragolumab administered as a single agent. Preliminary population-PK analysis estimated tiragolumab clearance at 0.283 L/day and linear elimination half-life of 16.4 days. Anti-drug antibodies (ADAs) to tiragolumab were not detected in the Phase Ia portion of Study GO30103. In the Phase Ib portion of the study, 3 of 145 evaluable patients (2.1%) were positive for ADAs. Preliminary limited data suggest that there was no apparent effect of tiragolumab ADAs on the pharmacokinetics of tiragolumab.

Refer to the Tiragolumab Investigator's Brochure for further details and the most current information.

Clinical Pharmacokinetics and Immunogenicity of Atezolizumab

Overall, atezolizumab exposures increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg, including the fixed dose of 1200 mg administered Q3W. The clearance and elimination half-life of atezolizumab was estimated to be 0.2 L/day and 27 days, respectively, based on a Phase I population-PK analysis that included 472 patients from Studies PCD4989g and JO28944. Anti-drug antibodies to atezolizumab have been observed in some patients at all dosing levels, but the presence of ADAs did not appear to have a clinically significant impact on pharmacokinetics, safety, or efficacy of atezolizumab at the 1200-mg dose.

As of the clinical cutoff date of 3 December 2018, preliminary PK data were available from patients treated with tiragolumab in combination with atezolizumab in the Phase Ib portion of Study GO30103. Overall, the exposures of atezolizumab or the presence of ADAs to atezolizumab were not altered in combination with tiragolumab in this study. Refer to the Tiragolumab Investigator's Brochure for further details and the most current information.

Refer to the Atezolizumab Investigator's Brochure for details on the clinical pharmacokinetics of atezolizumab.

1.7 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 mAb that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

[redacted]

Atezolizumab is approved for the treatment of NSCLC, small-cell lung cancer, urothelial carcinoma, triple-negative breast cancer, hepatocellular carcinoma, melanoma*, and alveolar soft part sarcoma.*

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

1.8 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.8.1 Study Rationale

Clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with metastatic cancer, including NSCLC. PD-L1/PD-1 inhibitors in the 1 L and second-line (2 L)-plus settings have demonstrated significant improvement in survival compared with standard chemotherapy, which has led to the recent approvals of these agents for the treatment of NSCLC and validates the inhibition of the PD-L1/PD-1 pathway for achieving clinical benefit in NSCLC. Furthermore, the safety profile of PD-L1 and PD-1 antibodies as monotherapy appears to be more tolerable than many of the chemotherapy doublet combinations given in the front-line setting, which are associated with substantial toxicities and are often poorly tolerated by elderly and patients with poor performance status.

Despite the robust activity observed with anti–PD-L1/PD-1 agents, durable clinical benefit appears limited to a minority of treated patients. Enrichment or selection strategies to identify those patients most likely to respond to PD-L1 and PD-1 inhibitors are still evolving, but one area has focused on PD-L1 selection of tumors, especially in earlier lines of therapy for metastatic NSCLC. Single-agent pembrolizumab is approved for the 1 L treatment of patients with NSCLC whose tumors express PD-L1 on the basis of a study that demonstrated that PD-L1 expression tends to enrich for increased efficacy (Mok et al. 2019). Recently, atezolizumab also demonstrated a statistically significant and clinically meaningful improvement in OS compared with chemotherapy as 1 L treatment of patients with metastatic NSCLC that expresses high PD-L1 in Study GO29431 (IMpower110) study (see Section 1.2.3). Based on the results from this study, atezolizumab monotherapy is approved in the European Union and United States, for the 1 L treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression (TC3 or IC3, with TC3 defined as PD-L1 staining on ≥ 50% of TC and IC3, defined as PD-L1 staining ≥10% on IC) with no *EGFR* or *ALK* genomic tumor aberrations.

As described in Section 1.3, it is hypothesized that the combination of anti-TIGIT with anti–PD-L1/PD-1 agents may result in activation of anti-tumor immune responses, leading to enhanced killing of TCs and improved clinical responses in patients with metastatic NSCLC than with either agent alone. Based on this hypothesis, the Phase II GO40290 (CITYSCAPE) study was designed to evaluate whether combining tiragolumab and atezolizumab would result in improved ORR and PFS compared with placebo and atezolizumab. At the primary analysis, the study demonstrated that the combination was associated with a higher ORR (55.2%) compared with placebo plus atezolizumab (17.2%) in patients with high PD-L1 expression (TPS ≥50%); investigator-assessed PFS was improved with the combination relative to placebo plus atezolizumab (unstratified HR=0.33; 95% CI: 0.15 to 0.72; median PFS: not reached vs. 3.9 months, respectively; see Section 1.6.2.3).

The results from the Phase II GO40290 study provide rationale to further evaluate the combination of tiragolumab and atezolizumab as a 1 L treatment for NSCLC in a larger Phase III study. Therefore, this current study (GO41717) is designed to evaluate whether the anti-tumor effects of atezolizumab, as measured by PFS and OS, may be improved with the addition of the anti-TIGIT antibody tiragolumab compared with placebo plus atezolizumab in patients with previously untreated, locally advanced or metastatic NSCLC who are selected on the basis of a minimum PD-L1 tumor expression. This study will enroll patients whose tumors are TPS ≥50% using the PD-L1 IHC 22C3 pharmDx assay, or TC3 or IC3 (with TC3 defined as staining on ≥50% of TCs and IC3 defined as staining ≥10% on ICs) using the VENTANA PD-L1 (SP142) Assay, or TC ≥50% using the investigational VENTANA PD-L1 (SP263) Companion Diagnostic (CDx) Assay, as assessed by central testing.

1.8.2 Benefit-Risk Assessment

This study will enroll patients with previously untreated locally advanced, unresectable, or metastatic PD–L1–selected NSCLC to receive either tiragolumab plus atezolizumab or to placebo plus atezolizumab in the control arm. Based on results from the Phase II GO40290 study, the combination of tiragolumab plus atezolizumab in the experimental arm can represent a potential valuable treatment option for patients with NSCLC that expresses high PD-L1 and can offer a reasonable benefit–risk balance for patients in this study.

To better understand the risks and benefits related to participation in this study, patients will be fully informed of the current 1 L treatment options for metastatic NSCLC. In some countries, the standard of care in the 1 L treatment of metastatic NSCLC without an *EGFR* mutation or *ALK* alteration remains a chemotherapy doublet often consisting of a platinum agent. Recently, PD-L1/PD-1–inhibitors in combination with platinum-based chemotherapy are also approved for the 1 L treatment of metastatic NSCLC, and as monotherapy in the United States as a 1 L treatment for metastatic NSCLC in patients whose tumors express PD-L1 (TPS ≥1%) and as monotherapy in the E.U. as a 1 L treatment in patients whose tumors express high PD-L1 (TPS ≥50%). Atezolizumab was recently approved in the United States as monotherapy for the first-line treatment of patients with metastatic NSCLC, whose tumors have a PD-L1 expression TC ≥50% or IC ≥10% by VENTANA PD-L1 (SP142) Assay and who do not have *EGFR* or *ALK* genomic tumor aberrations.

Given these available treatment options, patients will be informed that although single-agent atezolizumab is not currently approved in all countries for the 1 L treatment of metastatic NSCLC, the randomized Phase IiI GO29431 (IMpower110) study has recently shown that single-agent atezolizumab resulted in a statistically significant and clinically meaningful improvement in OS compared with chemotherapy as 1 L treatment of patients with metastatic NSCLC that expresses high PD-L1 (see Section 1.2.3). On the basis of these data, 1 L atezolizumab monotherapy has clinical efficacy in

patients with high PD-L1 metastatic NSCLC and is generally well tolerated as monotherapy (refer to the Atezolizumab Investigator's Brochure).

As described in Section 1.8.1, it is hypothesized that clinical activity in metastatic NSCLC may be enhanced with atezolizumab when combined with the anti-TIGIT antibody tiragolumab. Patients will be informed that the combination of tiragolumab plus atezolizumab has been studied in a Phase II study in metastatic PD-L1–selected NSCLC, and the combination showed increased ORR compared with atezolizumab alone, which was notable in patients with high PD-L1 expression (see Section 1.6.2.3). The combination of tiragolumab plus atezolizumab was also well tolerated. Adverse events with potentially immune-mediated causes were observed with a higher incidence in the tiragolumab plus atezolizumab arm in Study GO40290. However, the imbalance was mostly attributed to Grade 1–2 rash and IRRs (see Section 1.6.2.2). Grade 3–4 immune-mediated adverse events were similar between the treatment arms. To date, immune-mediated adverse events have been manageable with standard medical practice supplemented with corticosteroids, immunosuppressive agents, and/or hormone replacement therapy.

Given the mechanism of action for atezolizumab and tiragolumab, immune-mediated adverse events are potential overlapping toxicities associated with combination use of these two agents.

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, it is unclear whether or how systemic cancer therapies, such as chemotherapy, targeted therapy, or immunotherapy impact, the incidence or severity of SARS-CoV-2 infection.

A possible consequence of immune checkpoint inhibition may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-L1/PD-1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13; Frebel et al. 2012; Wykes and Lewin 2018; Schorer et al. 2020). However, there are insufficient and inconsistent clinical data to assess if outcome from SARS-CoV-2 infection is altered by cancer immunotherapy.

Severe SARS-CoV-2 infection appears to be associated with a cytokine-release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute SARS-CoV-2 infection while receiving atezolizumab and/or tiragolumab. At this time,

there is insufficient evidence for causal association between atezolizumab or tiragolumab and an increased risk of severe outcomes from SARS-CoV-2 infection.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with immune checkpoint inhibitors and clinical and radiologic features for SARS-CoV-2–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

There are limited data concerning the possible interactions between cancer immunotherapy treatment and COVID-19 vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies may positively or negatively impact the efficacy and safety of COVID-19 vaccination (SITC 2020).

Per recommendations of the National Comprehensive Cancer Network (NCCN) COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For patients enrolling in this study and receiving atezolizumab treatment, a decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

In alignment with clinical practice procedures, factors to consider when making the individualized decision for patients receiving atezolizumab treatment to receive COVID-19 vaccination include the following: the risk of SARS-CoV-2 infection and potential benefit from the vaccine, the general condition of the patient and potential complications associated with SARS-CoV-2 infection, underlying disease, and the severity of COVID-19 outbreak in a given area or region.

The Society for Immunotherapy of Cancer (SITC) and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines. When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such (see Section 4.4.1).

In this study, patients will be selected on the basis of high tumor tissue PD-L1 expression, as assessed by central testing. This study will enroll patients whose tumors are TPS $\geq$50% using the PD-L1 IHC 22C3 pharmDx assay, or TC3 or IC3 using the VENTANA PD-L1 (SP142) Assay, or TC $\geq$50% using the investigational VENTANA

PD-L1 (SP263) CDx Assay. Treatment with atezolizumab for all patients in this study offers the potential for clinical benefit in treatment-naive patients with metastatic NSCLC. Based on the results from the Phase II GO40290 study, the combination of tiragolumab with atezolizumab in this study may benefit patients with high expressing PD-L1 tumors beyond treatment with atezolizumab alone. Because the toxicities of atezolizumab and of the combination of tiragolumab plus atezolizumab appear to be similar and have been generally mild and transient in nature, patients may not have increased toxicity with the combination of tiragolumab plus atezolizumab. Therefore, based on the above data that patients will be selected for this study on the basis of high tumor PD-L1 expression, that all patients in the study will receive the PD-L1 inhibitor atezolizumab, and that the clinical data to date suggest that the combination of tiragolumab plus atezolizumab in patients with metastatic PD-L1–high NSCLC results in a clinically meaningful improvement in PFS and a higher ORR without increased toxicity, the overall benefit–risk ratio is considered to be appropriate for the study population.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated locally advanced, unresectable or metastatic PD-L1–selected NSCLC, with no known *EGFR* mutation or *ALK* translocation.

The study population is selected on the basis of a high tumor tissue PD-L1 expression, as assessed by central testing, defined by meeting at least one of the following thresholds specific to each assay: PD-L1 IHC 22C3 pharmDx assay (TPS $\geq$ 50%), VENTANA PD-L1 (SP142) Assay (TC3 or IC3), or investigational VENTANA PD-L1 (SP263) CDx Assay (TC $\geq$ 50%).

[redacted]

Furthermore, the evaluation will also be done in patients with high tumor PD-L1 expression, as determined by the investigational VENTANA PD-L1 (SP263) CDx Assay (TC $\geq$ 50%, defined as the secondary analysis set [SAS] for the purpose of hypothesis testing), and [redacted]

In this protocol, "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., tiragolumab plus atezolizumab and placebo plus atezolizumab).

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of tiragolumab plus atezolizumab compared with placebo plus atezolizumab on the basis of the following co-primary endpoints in the PAS:

- PFS after randomization, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first
- OS, defined as the time from randomization to death from any cause

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of tiragolumab plus atezolizumab compared with placebo plus atezolizumab on the basis of the following endpoints:

- Investigator-assessed PFS according to RECIST v1.1 and OS in the SAS
- Confirmed ORR, defined as the proportion of patients with a confirmed objective response (i.e., CR or PR on two consecutive occasions $\geq$4 weeks apart), as determined by the investigator according to RECIST v1.1
- DOR for patients with confirmed ORR, defined as the time from the first occurrence of a documented confirmed objective response to disease progression as determined by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first
- PFS rate at 6 months and 12 months, defined as the proportion of patients who have not experienced disease progression as determined by the investigator according to RECIST v1.1 or death from any cause at 6 months and at 12 months, respectively
- OS rate at 12 months and 24 months, defined as the proportion of patients who have not experienced death from any cause at 12 and 24 months, respectively
- Time to confirmed deterioration (TTCD) in patient-reported physical functioning and global health status/quality of life (GHS/QoL), as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-for-Cancer (QLQ-C30)

[redacted]

- [redacted]

- [redacted]

2.2 SAFETY OBJECTIVES

The safety objective for this study is to evaluate the safety and tolerability of tiragolumab plus atezolizumab compared with placebo plus atezolizumab on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0)
  - The severity of CRS will also be determined according to the American Society for Transplantation and Cellular Therapy (ASTCT) CRS consensus grading scale.

[redacted]

- [redacted]
- [redacted]
- [redacted]

2.3 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is to characterize pharmacokinetics of tiragolumab and atezolizumab on the basis of the following endpoint:

- Serum concentrations of tiragolumab and atezolizumab at specified timepoints

2.4 IMMUNOGENICITY OBJECTIVE

The immunogenicity objective for this study is to evaluate the immune response to tiragolumab plus atezolizumab on the basis of the following endpoints:

- Prevalence of ADAs to tiragolumab at baseline and incidence of ADAs to tiragolumab during the study
- Prevalence of ADAs to atezolizumab at baseline and incidence of ADAs to atezolizumab during the study

[redacted]

- [redacted]

[redacted]

[redacted]

- [redacted]

2.6 HEALTH STATUS UTILITY OBJECTIVE

The health status utility objective for this study is to evaluate the impact of health status utility scores of patients treated with tiragolumab plus atezolizumab compared with placebo plus atezolizumab on the basis of the following endpoint:

- Change in EQ-5D-5L index-based and visual analog scale (VAS) scores at specified timepoints during the study (including post-progression)

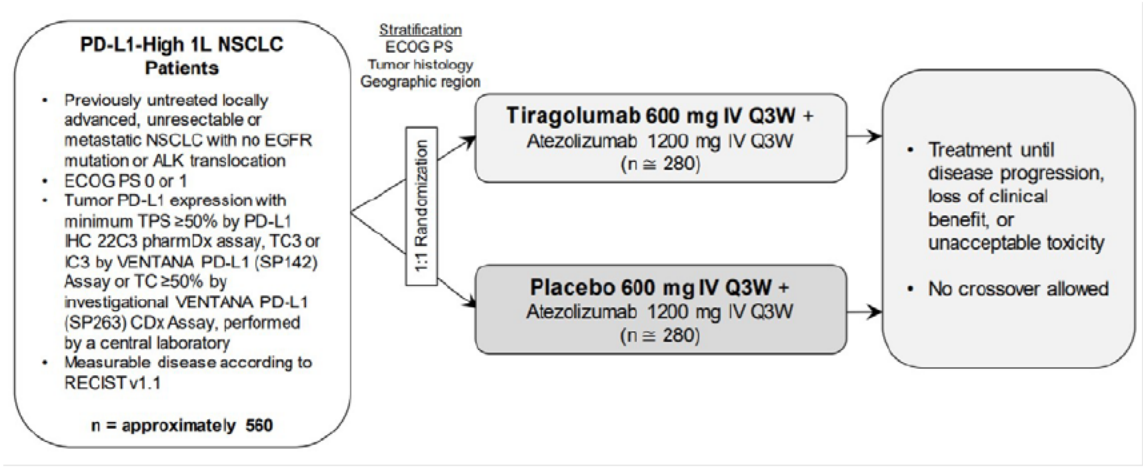
3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase III, randomized, double-blinded, placebo-controlled, global, multicenter study designed to evaluate the efficacy and safety of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated locally advanced, unresectable or metastatic PD-L1–selected NSCLC.

The study design is shown in Figure 1 and the schedule of assessments is provided in Appendix 1. The PK, immunogenicity, and biomarker sampling schedule is presented in Appendix 2.

Figure 1 Study Design



1 L = first-line; ALK = anaplastic lymphoma kinase (gene); CDx = companion diagnostic; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor gene; IC = immune cell; IHC = immunohistochemistry; NSCLC = non–small cell lung cancer; PAS = primary analysis set; PD-L1 = programmed death–ligand 1; PS = Performance Status; Q3W = every 3 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; TC = tumor cell; TPS = tumor proportion score.

Note: Approximately 560 patients with previously untreated, locally advanced unresectable or metastatic NSCLC that harbors high tumor PD-L1 expression, as assessed by central testing, using any of the three assays, TPS ≥ 50% by PD-L1 IHC 22C3 pharmDx assay, TC3 or IC3 by VENTANA PD-L1 (SP142) assay, or TC ≥ 50% by investigational VENTANA PD-L1 (SP263) CDx assay, will be enrolled globally. [redacted]

Male and female patients age ≥ 18 years with ECOG Performance Status of 0 or 1 who have previously untreated locally advanced, unresectable, or metastatic PD-L1–selected NSCLC are eligible.

After providing informed consent, patients will undergo screening procedures as outlined in the schedule of activities in Appendix 1. Patients who do not initially meet all eligibility criteria for participation in this study may qualify for one re-screening opportunity (for a total of two screenings per patient) at the investigator's discretion. [redacted] For patients who are rescreened, all eligibility criteria must be re-evaluated and screening assessments should be repeated as applicable to meet the eligibility criteria outlined in Sections 4.1.1 and 4.1.2. The investigator will record reasons for screen failure in the screening log (see Section 4.5.1).

During screening, tumor specimens from each potentially eligible patient will be prospectively tested for PD-L1 expression by a central laboratory using the PD-L1 IHC 22C3 pharmDx assay, VENTANA PD-L1 (SP142) Assay, and the investigational VENTANA PD-L1 (SP263) CDx Assay. Only patients with high tumor PD-L1 expression by any of the three assays: TPS ≥50% using the PD-L1 IHC 22C3 pharmDx assay, TC3 or IC3 using the VENTANA PD-L1 (SP142) Assay, or TC ≥ 50% using the investigational VENTANA PD-L1 (SP263) CDx Assay, by central assessment, will be eligible.

Patients whose tumors have a known *EGFR* mutation or *ALK* rearrangement will be excluded from this study. Patients with tumors of non-squamous histology with unknown *EGFR* or *ALK* mutational status will be required to be tested prior to enrollment (see inclusion criteria in Section 4.1.1). Patients with tumors of squamous histology who have an unknown *EGFR* or *ALK* mutational status will not be required to be tested (see inclusion criteria in Section 4.1.1).

Eligible patients will be randomized in a 1:1 ratio to receive either tiragolumab plus atezolizumab or placebo plus atezolizumab.

Eligible patients will be stratified by ECOG Performance Status (0 vs. 1), tumor histology (non-squamous vs. squamous), and geographic region of the enrolling site (Asia vs. non-Asia).

In the experimental arm, patients will receive atezolizumab at a fixed dose of 1200 mg administered by IV infusion Q3W on Day 1 of each 21-day cycle, followed by tiragolumab at a fixed dose of 600 mg administered to patients by IV infusion Q3W on Day 1 of each 21-day cycle.

In the control arm, patients will receive atezolizumab at a fixed dose of 1200 mg administered by IV infusion Q3W on Day 1 of each 21-day cycle, followed by placebo administered by IV infusion Q3W on Day 1 of each 21-day cycle.

Treatment may be continued as long as patients are experiencing clinical benefit, as assessed by the investigator, in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression after an integrated assessment of radiographic data, biopsy results (if available), and clinical status. Patients who meet the criteria for disease progression per RECIST v1.1 will be permitted to continue study treatment (tiragolumab plus atezolizumab or placebo plus atezolizumab) if they meet all of the criteria specified in Section 3.1.1 and provide written consent.

Patients will undergo tumor assessments at baseline and every 6 weeks (±7 days) for 48 weeks following Day 1 of Cycle 1 regardless of treatment delays (see Section 4.5.6 and Appendix 1). After the completion of the Week 48 tumor assessment, tumor assessments will be required every 9 weeks (±7 days) regardless of treatment delays until radiographic disease progression per RECIST v1.1, withdrawal of consent, death,

or study termination by the Sponsor, whichever occurs first. Patients who are treated beyond disease progression per RECIST v1.1 will undergo tumor assessments at the frequency described above until study treatment is discontinued. Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments at the frequency described above until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. In the absence of radiographic disease progression per RECIST v1.1, tumor assessments should continue regardless of whether a patient starts a new anti-cancer therapy.

Response will be assessed according to RECIST v1.1 (see Appendix 4). All primary imaging data used for tumor assessments will be collected by the Sponsor; centralized, blinded independent review of response endpoints by an Independent Review Facility (IRF) may be conducted.

[redacted]

During the study, patients will be asked to complete PRO questionnaires at the beginning of the study, during study treatment, at treatment discontinuation, and during survival follow-up (see Section 4.5.9 and Appendix 1).

During the study, serum samples will be collected to monitor tiragolumab and atezolizumab pharmacokinetics and to detect the presence of antibodies to tiragolumab and atezolizumab. [redacted].

Safety assessments will include the incidence, nature, and severity of adverse events, and other protocol-specified tests such as laboratory abnormalities that are deemed critical to the safety evaluation of the study.

After initiation of study treatment, all adverse events will be reported until [redacted] days after the final dose of study treatment [redacted], and serious adverse events will continue to be reported until [redacted] days after the final dose of study treatment [redacted]. In addition, adverse events of special interest will continue to be reported until [redacted] days after the final dose of study treatment, [redacted]. After this period, investigators should report any deaths or serious adverse events interest that are believed to be related to prior treatment with study drug(s). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is

assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or protocol-related procedures until a final outcome can be reported.

After study treatment discontinuation and disease progression per RECIST v1.1, survival follow-up information will be collected by means of telephone calls, patient medical records, and/or clinic visits approximately every 3 months or more frequently until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first (see Section 5.5). All patients will be periodically contacted for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from follow-up (this request must be documented in the source documents and signed by the investigator). If the patient withdraws from the study, study staff may use a public information source (e.g., county records) when permissible to obtain information about survival status.

3.1.1 Treatment after Disease Progression

During the study, patients who meet criteria for radiographic disease progression per RECIST v1.1 may continue study treatment at the investigator's discretion provided that the patients meet all of the following criteria:

- Evidence of clinical benefit, as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease
- No decline in ECOG Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patients must provide written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial radiographic progression per RECIST v1.1

For patients who receive study treatment beyond radiographic disease progression, new lesions with applicable measurements should be entered on the electronic Case Report Form (eCRF). Investigator assessment of overall tumor response at all timepoints will be based only on RECIST v1.1.

3.1.2 Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will evaluate safety data during the study. Sponsor affiliates will be excluded from iDMC membership. The iDMC will follow a charter that outlines the iDMC's roles and responsibilities.

Unblinded safety data will be reviewed on a periodic basis, approximately every 6 months from the time of enrollment of the first patient. All summaries and analyses for the iDMC review will be prepared by an independent Data Coordinating Center.

After reviewing the data, the iDMC will provide a recommendation to the Sponsor as described in the iDMC Charter. Final decisions will rest with the Sponsor.

Any outcomes of these data reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Boards/Ethics committees (IRBs/ECs).

3.2 END OF STUDY AND LENGTH OF STUDY

The end of study will occur when all of the following criteria have been met:

- The required number of deaths for the final analysis of OS has been observed (see Section 6.4.1).
- The last patient, last visit has occurred (the global and China extended enrollment phases).

In addition, the Sponsor may decide to terminate the study at any time. If the Sponsor decides to terminate the study, patients who are still receiving study treatment or undergoing survival follow-up may be enrolled in an extension study.

3.3 DURATION OF PARTICIPATION

The total duration of study participation for each individual is expected to be approximately 59 months.

3.4 RATIONALE FOR STUDY DESIGN

This Phase III study design is based on the hypothesis that the combination of tiragolumab plus atezolizumab may prolong PFS and OS compared with placebo plus atezolizumab in patients with previously untreated locally advanced, unresectable or metastatic NSCLC that has high PD-L1 expression.

3.4.1 Rationale for Testing Tiragolumab Plus Atezolizumab in Patients with PD-L1–Selected NSCLC

Although PD-L1/PD-1 inhibitors provide clinically meaningful benefit in the treatment of NSCLC, the majority of patients either do not respond to or progress on these immunotherapies. Therefore, there is a continuing need for rational combinations with immunotherapies in order to broaden the patient population who could derive benefit and to deepen and extend the response in the patient population that does respond.

TIGIT is a novel immune checkpoint inhibitor that is often co-expressed with PD-L1 on tumor-infiltrating lymphocytes. In nonclinical models, combined blockade of both TIGIT and PD-L1/PD-1 pathways demonstrated superior efficacy over the respective

single-agent treatments. It is hypothesized that the combination of an anti-TIGIT antibody, such as tiragolumab, with an anti–PD-L1/PD-1 antibody may result in activation of anti-tumor immune responses leading to enhanced killing of TCs and improved clinical responses.

In the Phase II study GO40290 in patients with 1 L NSCLC, an improvement in PFS and ORR was observed with the combination of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with high tumor PD-L1 expression (TPS ≥50%; see Section 1.6.2.3). The safety profile of tiragolumab plus atezolizumab was similar to that of single-agent atezolizumab. These data provide the rationale for further evaluating the efficacy of tiragolumab plus atezolizumab as a 1 L treatment of patients with metastatic NSCLC with high PD-L1 expression.

3.4.2 Rationale for Control Arm with Placebo Plus Atezolizumab in Patients with PD-L1–High NSCLC

For the reasons described in Section 1.8.2, patients with high tumor PD-L1 expression will be enrolled in this Phase III study. All patients, whether in the experimental arm or in the control arm, will receive atezolizumab.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.4.4 Rationale for Inclusion of Patients with Non-Squamous and Squamous NSCLC

Atezolizumab has shown significant clinical benefit in patients with metastatic NSCLC independent of histology. In the Phase III study GO28915 (OAK), OS was improved for patients treated with atezolizumab compared with docetaxel, with similar OS benefit observed in patients whose tumors were of non-squamous histology (HR = 0.73; 95% CI: 0.60 to 0.89) compared with patients whose tumors had squamous histology (HR = 0.73; 95% CI: 0.54 to 0.98; Rittmeyer et al. 2017). In the Phase III GO29431 (IMpower110) study, in patients with high PD-L1 expression, atezolizumab also demonstrated a clinically meaningful improvement in OS compared with platinum-based chemotherapy in patients whose tumors were of non-squamous histology (HR = 0.62; 95% CI: 0.40 to 0.96) or squamous histology (HR = 0.56; 95% CI: 0.23 to 1.37; Spigel et al. 2019).
In the Phase II GO40290 study, objective responses were observed with the combination of tiragolumab plus atezolizumab in patients whose tumors were of non-squamous or squamous histology (see Section 1.6.2.3), and suggest that tiragolumab plus atezolizumab are active in patients with metastatic NSCLC, independent of histology. Based on these data, patients with metastatic NSCLC of either non-squamous or squamous histology will be eligible to enroll in this study, and all patients will receive atezolizumab.

3.4.5 Rationale for Exclusion of Patients with an *EGFR* Mutation or *ALK* Translocation

Patients with tumors harboring an *EGFR* mutation or *ALK* translocation will not be eligible for this study. Genotype-directed therapy, rather than immunotherapy, remains the standard of care in the 1 L treatment setting for these patients. For patients with NSCLC (of mainly non-squamous histology) with an *EGFR* mutation, randomized Phase III studies of the *EGFR* inhibitors gefitinib, erlotinib, and afatinib showed significant improvement in PFS and ORR compared with platinum-doublet chemotherapy (Fukuoka et al. 2011; Rosell et al. 2012; Yang et al. 2012).
More recently, osimertinib, a third-generation *EGFR* inhibitor, demonstrated significant improvement in PFS compared with gefitinib and erlotinib (Soria et al. 2018).
For patients with metastatic NSCLC with *ALK* rearrangements, crizotinib and alectinib have demonstrated increased efficacy (Shaw et al. 2013; Peters et al. 2017).

When patients with metastatic NSCLC with *EGFR* mutations are treated with immunotherapy alone, there appeared to be no increased OS benefit.
In Study GO28915 (OAK), patients with metastatic NSCLC with *EGFR* mutation–positive disease had similar OS benefit with atezolizumab or with docetaxel (HR = 1.24; median OS 10.5 months with atezolizumab vs. 16.2 months with docetaxel), whereas patients with *EGFR* wild-type disease had improved OS with atezolizumab compared with

docetaxel (HR = 0.69; median 15.3 months vs. 9.5 months; Rittmeyer et al. 2017). Similarly, in the Phase III study (CheckMate-057) of nivolumab compared with docetaxel in the 2 L treatment of NSCLC, patients with NSCLC with *EGFR* mutation–positive disease had similar OS benefit with nivolumab or docetaxel (HR = 1.18) in contrast to patients with *EGFR* wild-type disease who had improved OS with nivolumab relative to docetaxel (HR = 0.66; Borghaei et al. 2015). Patients with NSCLC with *EGFR* mutation–positive disease were also excluded from the Phase III studies (KEYNOTE-024 and KEYNOTE-042) of pembrolizumab versus chemotherapy in the 1 L setting (Reck et al. 2016; Mok et al. 2019). It is hypothesized that this subgroup of patients with *EGFR* mutation–positive NSCLC may have decreased immunogenicity. Therefore, on the basis of the data above, patients with known *EGFR* mutations or *ALK* translocations will be excluded from the study.

[redacted]

[redacted]

[redacted]

[redacted]

3.4.7 Rationale for Progression-Free Survival and Overall Survival as Co-Primary Endpoints

In this study, the co-primary efficacy endpoints will be investigator-assessed PFS and OS. This study will test the hypothesis that treatment with tiragolumab and atezolizumab will prolong PFS and OS compared with treatment with placebo and atezolizumab.

Progression-free survival is a commonly used endpoint in oncology trials because it can reflect tumor growth and may be assessed before the evaluation of a survival benefit; additionally, its determination is generally not confounded by subsequent therapies. Meta-analyses have indicated that PFS can be considered a good measure of clinical benefit for patients with locally advanced or metastatic NSCLC (Laporte et al. 2013), especially if the magnitude of effect is large and the treatment has an acceptable benefit–risk profile compared with available therapies (FDA 2007; European Medicines Agency 2012).

Improvement in OS is generally accepted as the best measure of clinical benefit for patients with advanced/unresectable or metastatic lung cancer. Recent data also suggest that OS may be a more sensitive endpoint for CIT (Fehrenbacher et al. 2016).

3.4.8 Rationale for Biomarker Assessments

3.4.8.1 Rationale for Collection of Mandatory Archival and/or Pretreatment Biopsy Tumor Specimens

Published results suggest that expression of PD-L1 in tumors correlates with response to anti–PD-L1/PD-1 therapy (Topalian et al. 2012). This correlation was also observed with atezolizumab in NSCLC administered to patients as a single agent (Herbst et al. 2014; Besse et al. 2015; Horn et al. 2015; Spigel et al. 2015; Fehrenbacher et al. 2016; Rittmeyer et al. 2017), and in combination with chemotherapy in Study GO29436 (IMpower150; Reck et al. 2017). Similar observations have been reported for other PD-L1 or PD-1 inhibitors (Higgs et al. 2015; Muro et al. 2015; Seiwert et al. 2015).

In the Phase II GO40290 study in NSCLC, tiragolumab plus atezolizumab was associated with a clinically meaningful improvement in PFS and a higher ORR in patients with high PD-L1 expression (TPS $\geq$ 50% on the PD-L1 IHC 22C3 pharmDx assay) treated with tiragolumab plus atezolizumab compared with placebo plus atezolizumab.

In this Phase III study, archival and/or fresh tumor specimens from patients will be tested for PD-L1 expression by a central laboratory, and only patients with PD-L1high tumors (defined by expression of PD-L1 with the PD-L1 IHC 22C3 pharmDx assay as TPS $\geq$ 50%, VENTANA PD-L1 [SP142] Assay as TC3 or IC3, or investigational VENTANA PD-L1 [SP263] CDx Assay as TC $\geq$ 50%) will be enrolled. The efficacy endpoints will be analyzed in the PAS, defined by the PD-L1 IHC 22C3 pharmDx assay. In addition, as part of secondary efficacy analyses, investigator-assessed PFS and OS will also be analyzed in the TC $\geq$ 50% population using the investigational VENTANA PD-L1 (SP263) CDx Assay (SAS). Investigator-assessed PFS and OS will also be analyzed as part of exploratory analyses in the TC3 or IC3 population using the VENTANA PD-L1 (SP142) Assay.

[redacted]

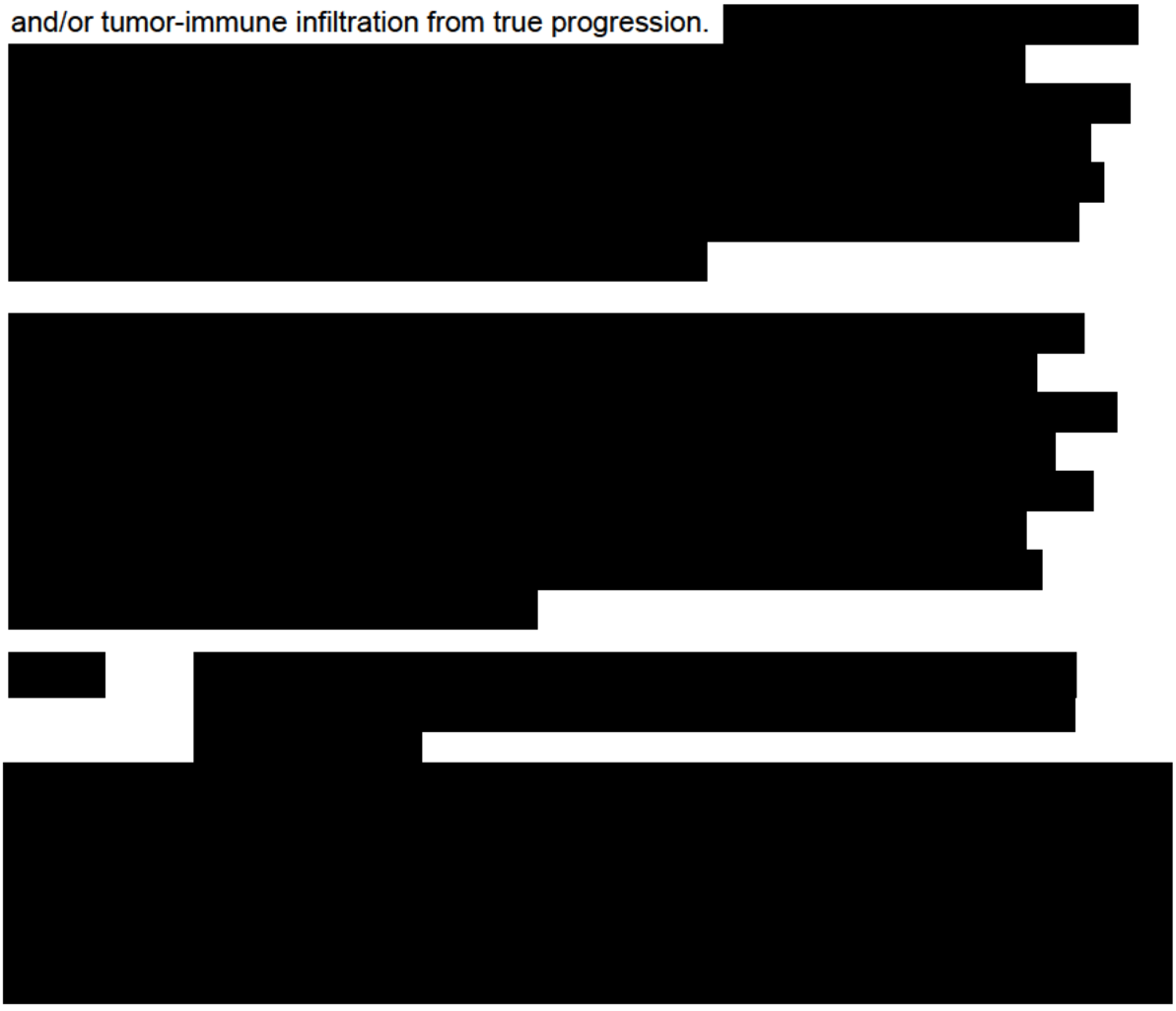
3.4.8.2 Rationale for Collection of Blood Samples for Biomarker Analyses

Blood samples for biomarker analyses will be collected at baseline, during the study treatment period, and at study treatment discontinuation. [redacted]

3.4.8.3 Rationale for Collection of Optional Tumor Specimens, Including a Biopsy at the Time of Radiographic Progression

Patients agreeing to optional tumor biopsies may undergo tissue collection at any time, if clinically feasible. However, it is preferable that optional tumor biopsies be collected at the first evidence of radiographic response, or at the first evidence of radiographic disease progression during treatment (within 40 days of radiographic progression or at the start of the next anti-cancer treatment, whichever is sooner). Anti-tumor immune responses such as those associated with tiragolumab and/or atezolizumab may result in objective responses that are delayed and can be preceded by initial apparent radiographic progression. This initial apparent progression may occur as a result of either delayed anti-tumor activity and/or robust tumor immune infiltration with a concomitant increase in tumor size. In addition, lesions that would otherwise be undetectable with conventional imaging (i.e., micrometastatic disease) may increase in size as a result of these processes (Hales et al. 2010).

Therefore, a tumor biopsy performed in patients at the time of first radiographic progression will evaluate the utility of tissue biopsy in distinguishing pseudoprogression and/or tumor-immune infiltration from true progression.



[redacted]

[redacted]

3.4.9 Rationale for Allowing Patients to Continue Study Treatment Beyond Disease Progression per RECIST v1.1

Conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) may not necessarily reflect therapeutic failure. Because of the potential for pseudoprogression and/or tumor immune infiltration, this study will allow patients randomized to receive either tiragolumab plus atezolizumab or placebo plus atezolizumab to continue to receive study treatment after apparent radiographic progression, provided the benefit–risk ratio is judged to be favorable. Patients should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status (see Section 3.1.1).

3.4.10 Rationale for Patient-Reported Outcome Assessments

In the treatment of lung cancer, it is important to both increase survival and palliate symptoms because disease symptoms have negative effects on HRQoL (Hyde and Hyde 1974; Hopwood and Stephens 1995; Sarna et al. 2004). This is especially true for studies that have PFS as a primary endpoint, to inform how delays in radiographic progression might be associated with delays in clinical progression of symptoms and their interference on functioning, including maintenance of low disease burden.

In addition, many of the most frequent adverse events attributed to tiragolumab and atezolizumab (e.g., fatigue, rash, nausea) are symptoms directly reportable by patients;

therefore, patients' reporting of their experience with these symptoms will complement the evaluation of treatment tolerability (King-Kallimanis et al. 2019).

This study includes use of validated patient-reported measures of symptom severity, and symptom impact on functioning, including HRQoL: the EORTC QLQ-C30, EORTC IL46 (see Appendix 5), [redacted]
Data generated from these instruments will inform patients' experience with disease burden and treatment tolerability as part of the totality of evidence generated to inform the risk benefit of tiragolumab and atezolizumab.

The EQ-5D-5L (see Appendix 7) is also included in this study to generate utility scores for use in economic models for reimbursement.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 560 patients with previously untreated, locally advanced unresectable or metastatic NSCLC that is PD-L1 selective will be enrolled at approximately 150 sites globally.

[redacted]

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- ECOG Performance Status of 0 or 1 (see Appendix 3)
- Histologically or cytologically documented locally advanced or recurrent NSCLC that is not eligible for curative surgery and/or definitive radiotherapy with or without chemotherapy, or metastatic Stage IV NSCLC (per the Union Internationale Contre le Cancer/American Joint Committee on Cancer staging system, 8th edition; Detterbeck et al. 2017) of either non-squamous or squamous histology

[redacted]

- No prior systemic treatment for metastatic NSCLC

[redacted]

- Tumor PD-L1 expression with a TPS $\geq$ 50% as determined by the PD-L1 IHC 22C3 pharmDx assay, or TC3 or IC3 as determined by the VENTANA PD-L1 (SP142) Assay, or TC $\geq$ 50% as determined by the investigational VENTANA PD-L1 (SP263) CDx Assay, documented through central testing of a representative tumor tissue, in either a previously obtained archival tumor tissue or tissue obtained from a biopsy at prescreening/screening

[redacted]

[redacted]

- Measurable disease per RECIST v1.1 (see Appendix 4)

  [redacted]

- Life expectancy ≥ 12 weeks
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment (Day 1 of Cycle 1):

  [redacted]

  - [redacted]
  - [redacted]
  - [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period, and for 90 days after the final dose of tiragolumab/placebo and 5 months after the final dose of atezolizumab.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 90 days after the final dose of tiragolumab/placebo to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

- For patients enrolled in the extended China enrollment phase: current resident of mainland China or Taiwan and of Chinese ancestry

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- NSCLC known to have a mutation in the *EGFR* gene or an *ALK* fusion oncogene
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Spinal cord compression not definitively treated with surgery and/or radiation, and/or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥2 weeks prior to randomization
- Leptomeningeal disease

- Uncontrolled tumor-related pain
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once a month or more frequently)
- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected calcium greater than ULN)
- Active or history of autoimmune disease or immune deficiency,
  -
  -
  -
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis

- Active tuberculosis
- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, and inherited liver disease, or current alcohol abuse
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina



- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
- History of malignancy other than NSCLC within 5 years prior to randomization, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate $>$ 90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal breast carcinoma in situ, or Stage I uterine cancer
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that, in the opinion of the investigator, could impact patient safety
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment



- Prior allogeneic stem cell or solid organ transplantation
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during study treatment or within 5 months after the final dose of study treatment
- Current treatment with anti-viral therapy for HBV or HCV
- 

[redacted]

- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-cytotoxic T lymphocyte–associated protein 4, anti-TIGIT, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, IFN and IL-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
  - [redacted]
  - [redacted]
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to CHO cell products or to any component of the tiragolumab or atezolizumab formulation
- Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after the final dose of study treatment

[redacted]

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a Phase III, randomized, double-blinded, placebo-controlled study. After written informed consent has been obtained and eligibility has been established (including determination of tumor PD-L1 status by central testing), the study site will obtain the patient's identification number and blinded treatment assignment from the interactive voice or web-based response system (IxRS).

Patients will be randomized to receive either tiragolumab plus atezolizumab or placebo plus atezolizumab. Randomization will occur in a 1:1 ratio through the use of a

permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified according to the following criteria:

- ECOG Performance Status (0 vs. 1)
- Tumor histology of NSCLC (non-squamous vs. squamous)
- Geographic region of the enrolling site (Asia vs. non-Asia)

Patients should receive their first dose of study drug on the day of randomization if possible.

4.2.2 Blinding

Study site personnel and patients will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment,

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The treatment code should not be broken except in emergency situations.

[redacted]

[redacted]

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are tiragolumab, placebo, and atezolizumab. All patients will receive atezolizumab in combination with either tiragolumab or with placebo. *Appendix 11 identifies all IMPs and auxiliary medicinal products for this study.*

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Tiragolumab and Placebo

Tiragolumab and placebo will be supplied by the Sponsor as a sterile liquid in a single-use, [redacted]-mL glass vial. The vial contains approximately [redacted] mL (600 mg) of tiragolumab or placebo solution.

For further information on the formulation and handling of tiragolumab and placebo, refer to the pharmacy manual and/or the Tiragolumab Investigator's Brochure.

4.3.1.2 Atezolizumab

Atezolizumab will be supplied by the Sponsor as a sterile liquid in a single-use, [redacted]-mL glass vial. The vial contains approximately [redacted] mL (1200 mg) of atezolizumab solution.

For information on the formulation and handling of atezolizumab, refer to the pharmacy manual and the Atezolizumab Investigator's Brochure.

4.3.2 Study Treatment Dosage, Administration, and Compliance

On Day 1 of each 21-day cycle, all eligible patients will be administered infusion of study treatments in the following order:

- Arm A: atezolizumab 1200 mg IV→tiragolumab 600 mg IV
- Arm B: atezolizumab 1200 mg IV→placebo 600 mg IV

[redacted]

Administration of tiragolumab/placebo and atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 9. Guidelines for medical management of IRRs are provided in Appendix 10.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Tiragolumab/placebo (600 mg) and atezolizumab (1200 mg) will be administered at a fixed dose. Information on study drug administration (including date of administration, dose administered, infusion start and stop time) should be noted on the Study Drug Administration eCRF. Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.4 and Appendix 10.

4.3.2.1 Atezolizumab

All patients will receive 1200 mg atezolizumab administered by IV infusion on Day 1 of each 21-day cycle (see Section 3.4.6.1). The atezolizumab dose is fixed and is not dependent on body weight.

Atezolizumab infusions will be administered per the instructions outlined in Table 2.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation are provided in Section 4.6.1, Section 5.1.4, and Appendix 10.

For further details on dose preparation, storage, and administration instructions for atezolizumab, refer to the pharmacy manual and/or the Atezolizumab Investigator's Brochure.

4.3.2.2 Tiragolumab/Placebo

Following the administration of atezolizumab [redacted] (see Table 2), patients will receive 600 mg tiragolumab/placebo administered by IV infusion on Day 1 of each 21-day cycle (see Section 3.4.6.2). The tiragolumab/placebo dose is fixed and is not dependent on body weight.

Tiragolumab/placebo infusions will be administered per the instructions outlined in Table 2.

No dose modification for tiragolumab/placebo is allowed. Guidelines for treatment interruption or discontinuation are provided in Section 4.6.1, Section 5.1.4, and Appendix 10.

For further details on dose preparation, storage, and administration instructions for tiragolumab/placebo, refer to the pharmacy manual and/or the Tiragolumab Investigator's Brochure.

Table 2 Administration of First and Subsequent Infusions of Atezolizumab and Tiragolumab/Placebo

Study drug	First Infusion	Subsequent Infusions
Atezolizumab infusion	• No premedication is allowed for the first infusion of atezolizumab. • Record the patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) within 60 minutes prior to starting the infusion. • Infuse atezolizumab over 60 (±15) minutes. • Record the patient's vital signs every 15 (±5) minutes during the infusion.	• If the patient experienced an IRR during any previous infusion of atezolizumab, premedication with an antihistamine and/or antipyretic may be administered for subsequent infusions at the discretion of the investigator. • Record the patient's vital signs within 60 minutes prior to starting the infusion. • If the patient tolerated the first infusion of atezolizumab well without an IRR, the next infusion of atezolizumab may be infused over 30 (±10) minutes. • If no reaction occurs, continue subsequent infusions of atezolizumab over 30 (±10) minutes. • If the patient experienced an IRR with the previous infusion, the next infusion of atezolizumab should be administered over 60 (±15) minutes. • Record vital signs during the infusion if clinically indicated.
Observation period after infusion of atezolizumab	• After the infusion of atezolizumab, the patient begins a 60-minute observation period. • Record the patient's vital signs at 30 (±10) minutes after the infusion. • Patients will be informed about the possibility of delayed post-infusion symptoms and will be instructed to contact the investigator if they develop such symptoms.	• If the patient tolerated the previous infusion of atezolizumab well without an IRR, the observation period after subsequent infusions may be reduced to 30 minutes. • If the patient experienced an IRR in the previous infusion, the observation period should be 60 minutes. • If clinically indicated, record the patient's vital signs at 30 (±10) minutes after the infusion].

Table 2 Administration of First and Subsequent Infusions of Atezolizumab and Tiragolumab/Placebo (cont.)

	First Infusion	Subsequent Infusions
Infusion of tiragolumab/ placebo	• No premedication is allowed for the first infusion of tiragolumab/placebo. • Record the patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) within [redacted] minutes prior to starting the infusion. • Infuse tiragolumab/placebo over [redacted] minutes. • Record the patient's vital signs every [redacted] minutes during the infusion.	• If the patient experienced an IRR during any previous infusion of tiragolumab/placebo, [redacted] may be administered for subsequent infusions at the discretion of the investigator. • Record the patient's vital signs within [redacted] minutes prior to starting the infusion. • If the patient tolerated the first infusion of tiragolumab/placebo well without an IRR, the next infusion of tiragolumab/placebo may be infused over [redacted] minutes. • If no reaction occurs, continue subsequent infusions of tiragolumab/placebo over [redacted] minutes. • If the patient experienced an IRR with the previous infusion, the next infusion of tiragolumab/placebo should be administered over [redacted] minutes. • Record vital signs during the infusion if clinically indicated.
Observation period after infusion of tiragolumab/ placebo	• After the infusion of tiragolumab/placebo, the patient begins a [redacted]-minute observation period. • Record the patient's vital signs at [redacted] minutes after the infusion. • Patients will be informed about the possibility of delayed post-infusion symptoms and will be instructed to contact the investigator if they develop such symptoms.	• If the patient tolerated the previous infusion of tiragolumab/placebo well without an IRR, the observation period after subsequent infusions may be reduced to [redacted] minutes. • If the patient experienced an IRR with the previous infusion, the observation period should be [redacted] minutes. • If clinically indicated, record the patient's vital signs at [redacted] minutes after the infusion.

IRR = infusion-related reaction.

Guidelines for the medical management of IRRs are provided in Appendix 10.

4.3.2.3 Atezolizumab and Tiragolumab/Placebo

The following rules apply as long as neither atezolizumab nor tiragolumab/placebo has been permanently discontinued:

- [redacted]
- [redacted]

Guidelines for treatment interruption or discontinuation are provided in Sections 4.6.1 and 5.1.4.

4.3.3 Investigational Medicinal Product Accountability

All IMPs (tiragolumab/placebo and atezolizumab) required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

[redacted]

[redacted]

[redacted]

Refer to the pharmacy manual for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to Tiragolumab and/or Atezolizumab

Patients may be eligible to receive tiragolumab and/or atezolizumab as part of a post-trial access program or an extension study as described in Section 3.2. The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

[redacted]

[redacted]

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 4.4.2 and 4.4.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 9).

4.4.2 Cautionary Therapy

4.4.2.1 Corticosteroids, Immunosuppressive Medications, and TNF-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with tiragolumab and/or atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with tiragolumab and/or atezolizumab therapy (see Appendix 10 for details).

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 4.4.3) may be used during the study at the discretion of the investigator.

4.4.3 Prohibited Therapy

[redacted]

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1 and Appendix 2. All activities should be performed and documented for each patient.

Screening tests and evaluations will be performed within 28 days prior to Day 1 of Cycle 1. [redacted]

All treatment visits must occur ±3 days from the scheduled date unless otherwise noted. All assessments will be performed on the day of the specified visit unless a time window is specified. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment infusion unless otherwise noted.

[redacted]

Screening assessments performed ≤96 hours before Day 1 of Cycle 1 are not required to be repeated on Day 1 of Cycle 1. The following assessments may be performed ≤96 hours before Day 1 of each cycle:

- [redacted]
- [redacted]
- [redacted]

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Prior to signing the main Informed Consent Form for the study, patients may consent to the collection of tumor tissue (archival or newly obtained by means of biopsy) for determination of PD-L1 expression by signing a Prescreening Informed Consent Form. Patients with non-squamous NSCLC may also allow for central evaluation of *EGFR* and/or *ALK* status.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Patients who show apparent radiographic disease progression per RECIST v1.1 at a tumor response evaluation and are eligible and willing to continue study treatment beyond disease progression must sign consent at that time to acknowledge deferring other treatment options in favor of continuing study treatment.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures) and lung cancer mutational status (e.g., *EGFR* and *ALK*), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an

interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination should be performed at screening and will include an evaluation of the patient's weight and height, the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified post-baseline visits and as clinically indicated (see Appendix 1). Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

See Table 2 for details on the measurements of vital signs during study treatment.

4.5.5 Performance Status

Performance status will be measured using the ECOG Performance Status at baseline and will be assessed at regular intervals throughout the study (see Appendix 1).
For further details, see Appendix 3.

4.5.6 Tumor and Response Evaluations

Screening and subsequent tumor assessments must include CT scans of the chest and abdomen (with IV contrast unless contraindicated and oral contrast as appropriate per institutional standards). A CT scan with contrast of the pelvis is required at screening and as clinically indicated or as per local standard of care at subsequent response evaluations. Magnetic resonance imaging (MRI) scans with contrast of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest may be used in patients for whom CT scans with IV contrast are contraindicated (i.e., patients with iodine-based contrast allergy or impaired renal clearance).

A CT scan with contrast or MRI scan with contrast (if CT contrast is contraindicated) of the head must be performed at screening to evaluate CNS metastasis in all patients. If a CT scan with contrast is performed and the presence of brain metastases is considered equivocal, an MRI scan of the head is required to confirm or refute the diagnosis of CNS

metastases at baseline. Patients with active or untreated CNS metastases are not eligible for the study (see Section 4.1.2).

If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full contrast diagnostic CT scan.

Further investigations such as bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease according to RECIST v1.1 may be used.

[redacted]

All known sites of disease, including measurable and/or non-measurable disease, must be documented at screening and re-assessed at each subsequent tumor evaluation.

[redacted] The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). Patients will undergo tumor assessments at baseline and at every 6 weeks (±7 days) for 48 weeks following Day 1 of Cycle 1, regardless of treatment delays. After the completion of the Week 48 tumor assessment, tumor assessment will be required every 9 weeks (±7 days) regardless of treatment delays, until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for patients who continue study treatment after disease progression per RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first (see Appendix 1). At the investigator's discretion, scans may be performed at any time if progressive disease or loss of clinical benefit is suspected.

Response will be assessed by the investigator on the imaging modalities detailed above, using RECIST v1.1 (see Appendix 4). The investigator's assessment of overall tumor response at all timepoints should only be based on RECIST v1.1. Assessments should be performed by the same evaluator if possible to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

Study treatment may be continued as long as patients are experiencing clinical benefit as assessed by the investigator in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression after an integrated assessment of radiographic data, biopsy results (if available), and clinical status. Patients who meet criteria for disease progression per RECIST v1.1 will be permitted to continue study

treatment (tiragolumab plus atezolizumab or placebo plus atezolizumab) if they meet all of the criteria specified in Section 3.1.1 and provide written consent.

Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments at the frequency described above until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by Sponsor, whichever occurs first. Patients who start a new anti-cancer therapy in the absence of radiographic disease progression per RECIST v1.1 will continue tumor assessments at the frequency described above until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH
- Coagulation: INR or aPTT
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3; or total T3 at sites free T3 is not performed), and free thyroxine (also known as T4)
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]
- [redacted]

- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. During the study, urine pregnancy tests will be performed on Day 1 of every cycle. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).
- Urinalysis: pH, specific gravity, glucose, protein, ketones, blood; dipstick permitted

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis. Instruction manual and supply kits will be provided for these central assessments. Refer to the laboratory manual for additional details on sample handling.

Assessments Performed on Blood Samples

The following assessments will be performed on the blood samples:

- PK assays

  Serum samples will be obtained for measurement of tiragolumab or atezolizumab concentrations using validated immunoassays.
- ADA assays

  Serum samples will be obtained for measurement of ADAs to tiragolumab or to atezolizumab using validated assays.
- [redacted]
  - [redacted]

- [redacted]

- Auto-antibody assays
  - [redacted]

Assessments Performed on Tumor Samples

The following assessments will be performed on tumor samples:

- [redacted]
- Biomarker assays in archival or fresh tumor tissue samples will be analyzed for determination of eligibility.
  - [redacted]
  - [redacted]
  - [redacted] The availability of archival tumor tissue must be confirmed prior to study entry.

  - [redacted]
  - [redacted]

- For patients with non-squamous NSCLC, if *EGFR* and/or *ALK* status is unknown, these must be assessed locally or at a central laboratory for determination of study eligibility (see Section 4.1.2 for exclusion criteria). If samples are submitted for central testing, [redacted] (see additional details in the laboratory manual).
- Biomarker assays in optional tumor biopsies
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

[redacted] Guided by clinical and nonclinical data, additional exploratory research to evaluate tumor PD biomarkers and potential predictive biomarkers, to understand mechanism of action of the drug, and of disease biology using assays for analysis of proteins, RNA, and DNA may be performed. Tumor tissue and blood samples collected in this study may be used for NGS techniques to identify mutations (somatic mutations on tumor tissue and blood and possibly germline mutations on blood [germline analysis of blood is contingent upon site approval]).

These NGS methods may include WGS or WES of tissue and blood samples, but WGS or WES of blood samples will be performed only at participating sites (see Section 4.5.10).

Screening tumor tissue samples, including those collected from patients who do not enroll in the study, may be used for future research and/or development of disease-related tests or tools.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

[redacted]

- [redacted].
- [redacted]
- [redacted]
- [redacted]

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.8 Electrocardiograms

An ECG is required at screening, and as clinically indicated during the study.

[redacted]

[redacted]

4.5.9 Clinical Outcome Assessments

Patient-reported outcome data will be collected to document the treatment benefit and more fully characterize the clinical profile of tiragolumab plus atezolizumab. Patient-reported outcome data will be collected using the following instruments: EORTC QLQ-C30, a single item from the EORTC IL46, [redacted], and the EQ-5D-5L.

4.5.9.1 Data Collection Methods for Clinical Outcome Assessments

Paper versions of the PRO instruments will be self-administered by patients during the treatment period and interviewer administered by site personnel to the patient over the telephone during follow-up visits in order that data may be collected without mandating that patients travel to the clinical site (see schedule of activities in Appendix 1). Patient-reported outcome data will be entered into the study database by the site personnel. The questionnaires will be translated into the local language as required. For patients who are unable to return to the clinic because of government restrictions or personal safety or during the study follow-up period, PROs may be completed by means of a telephone call; source documentation should be obtained that includes, among other information, the questionnaires administered via telephone.

To ensure instrument validity and that data standards meet health authority requirements, questionnaires scheduled for administration during a clinic visit will be completed in their entirety by the patient prior to receiving any information on disease status, prior to the performance of non-PRO assessments that could bias patients' answers, and prior to the administration of study treatment, unless otherwise specified.

PROs should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.
- Site staff should review all completed instruments and should ask the patient to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the patient to complete the item or confirm that the item was intentionally left blank.

[redacted]

The Sponsor will not derive adverse events reports from PRO data (see Section 5.3.5.13).

4.5.9.2 Description of Clinical Outcome Assessment Instruments EORTC QLQ-C30 and EORTC IL46

The EORTC QLQ-C30 is a validated, reliable self-reported measure (Aaronson et al. 1993; Fitzsimmons et al. 1999; see Appendix 5). It consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, and pain), GHS/QoL, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The functioning and symptoms items are scored on a 4-point scale that ranges from "not at all" to "very much," and the GHS/QoL items are scored on a 7-point scale that ranges from "very poor" to "excellent." The EORTC QLQ-C30 module takes approximately 10 minutes to complete.

The EORTC QLQ-C30 is a validated and reliable self-reported measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) that consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, and pain), GHS/QoL, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scale scores can be obtained for the multi-item scales.
The EORTC QLQ C-30 module takes approximately 15 minutes to complete.
In addition, EORTC IL46 will be collected. This validated single-item question that assesses overall side effect impact (see Appendix 5).

PRO-CTCAE

The PRO-CTCAE is a validated item bank that is used to characterize the presence, frequency of occurrence, severity, and/or degree of interference with daily function of 78 patient-reportable symptomatic treatment toxicities (Basch et al. 2014; Dueck et al. 2015). The PRO-CTCAE contains 124 questions that are rated either dichotomously (for determination of presence vs. absence) or on a 5-point Likert scale (for determination of frequency of occurrence, severity, and interference with daily function). Treatment toxicities can occur with observable signs (e.g., vomiting) or non-observable symptoms (e.g., nausea). The standard PRO-CTCAE recall period is the previous [redacted] days. A subset of [redacted] symptoms that were deemed most applicable to the current treatments were selected for this study (see Appendix 6). The PRO-CTCAE takes approximately 10 minutes to complete.

EQ-5D-5L

The EQ-5D-5L is a validated self-reported health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013; see Appendix 7). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as VAS that measures health state. The EQ-5D-5L is designed to capture the patient's current health status. Published weighting systems

allow for creation of a single composite score of the patient's health status.
The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

4.5.10 Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing (for Patients at Participating Sites Only)

At participating sites, blood samples will be collected for DNA extraction [redacted] or WES to identify germline variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety.
DNA extracted from blood may be compared with DNA extracted from tissue to identify somatic variants by distinguishing germline variants from somatic variants. The samples may be sent to one or more laboratories for analysis.

[redacted]

[redacted]

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

[redacted]

See Section 4.5.12.6 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.11 Optional Tumor Biopsies

Consenting patients will undergo optional tumor biopsies at the investigator's discretion at any time (if deemed clinically feasible by the investigator). It is preferable that optional tumor biopsies be collected at the first evidence of radiographic response, or at the first evidence of radiographic disease progression during treatment (within 40 days of radiographic progression or at the start of the next anti-cancer treatment, whichever is sooner). Samples collected by means of resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

The Informed Consent Form will contain a separate section that addresses optional biopsies. A separate, specific signature will be required to document a patient's agreement to undergo optional biopsies. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by signing the Optional Biopsy Sample Informed Consent Form.

Samples may be used for exploratory biomarker research as described in Section 4.5.12. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Refer to Section 4.5.12.3 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.12 Optional Samples for Research Biosample Repository

4.5.12.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, and peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.12) will not be applicable at that site.

4.5.12.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to tiragolumab, atezolizumab, NSCLC, or drug safety:

- Leftover blood, serum, plasma, and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, and peptides), including leftover tissue samples from medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the study
- Optional blood sample for DNA extraction collected at any time during the study



Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.12.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.12.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.12.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the

Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.12.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Use of another non-protocol–specified anti-cancer therapy
- Pregnancy
- Radiographic disease progression per RECIST v1.1 (unless study treatment is continued beyond radiographic progression)

- For patients treated beyond radiographic disease progression per RECIST v1.1, loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease; see Section 3.1.1 for details)

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a treatment discontinuation visit ≤30 days after the final dose of study treatment (see Appendix 1). The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease per RECIST v1.1 will continue to undergo tumor response assessments and PRO assessments as outlined in the schedule of activities (see Appendix 1).

[redacted]

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

[redacted]

[redacted]

4.6.3 Partial Withdrawal from Study

[redacted]

4.6.4 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.5 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF STUDY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on anticipated mechanism of action, results from nonclinical studies, published data on similar molecules, clinical experience with tiragolumab alone and in combination with atezolizumab in Phase I and II studies, and the clinical safety profile of atezolizumab as a single agent. The anticipated important safety risks for atezolizumab and tiragolumab in combination with atezolizumab are outlined below (see Sections 5.1.2 and 5.1.3, respectively). Refer to the Tiragolumab Investigator's Brochure and the Atezolizumab Investigator's Brochure for a complete summary of safety information for each respective study drug.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of tiragolumab/placebo and atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Guidelines for managing patients who experience anticipated adverse events, including criteria for treatment interruption or discontinuation, are provided in Appendix 10. See Sections 5.2–5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

Patients with active infection are excluded from study participation. In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) prior to and during study participation should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

An iDMC will periodically review safety data during the study (see Section 3.1.2).

5.1.1 Risks Associated with Tiragolumab

[redacted] Although clinical evaluation of tiragolumab is limited and not all risks are known, as an antagonist of TIGIT, tiragolumab is anticipated to enhance T-cell and NK-cell proliferation, survival,

and function. Therefore, tiragolumab may increase the risk of autoimmune inflammation (also described as immune-mediated adverse events).

See Appendix 10 of the protocol and Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of anticipated safety risks for tiragolumab.

5.1.1.1 Infusion-Related Reactions

Because tiragolumab is a therapeutic mAb and targets immune cells, IRRs associated with hypersensitivity reactions, target-mediated cytokine release, and/or emergent ADAs may occur. Clinical signs and symptoms of such reactions may include rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.

Infusion-related reactions have been reported in patients treated with tiragolumab, with or without atezolizumab. The majority of events were mild to moderate and manageable.

[redacted]

See Section 4.3.2 for detailed guidance on the administration of atezolizumab and tiragolumab/placebo in this study. See Appendix 9 for guidance on anaphylaxis precautions, and Appendix 10 for guidance on the management of IRRs.

[redacted]

The use of tiragolumab to block the immune inhibitory receptor TIGIT serves to increase a baseline T-cell and NK-cell immune response, especially in combination with other checkpoint inhibitors (i.e., atezolizumab). [redacted]

[redacted]

5.1.1.3 Lymphopenia

[redacted] Lymphopenia is a potential risk with tiragolumab. Transient decreases in lymphocyte count without clinical sequelae have been observed in patients treated with tiragolumab, with or without atezolizumab. Patients with a lymphocyte count $<$ 500 cells/mL will be excluded from this study (see Section 4.1.2), and CBCs will be monitored regularly during the study (see Appendix 1).

5.1.1.4 Immune-Mediated Adverse Events

Nonclinical models have suggested a role of TIGIT signaling interruption in autoimmunity. In a knockout model (TIGIT–/–), loss of TIGIT signaling resulted in hyperproliferative T-cell responses and exacerbation of experimental autoimmune encephalitis (EAE). TIGIT–/– and wild-type B6 mice were immunized with myelin oligodendrocyte glycoprotein peptide in an EAE using suboptimal doses. In contrast to the wild-type B6 mice, the majority of the TIGIT–/–mice developed severe EAE (Joller et al. 2011).

Clinical experience with therapeutic agents intended to enhance anti-tumor T-cell responses has demonstrated that development of autoimmune inflammatory conditions is a general risk and may therefore be considered a potential risk of tiragolumab. Such immune-mediated adverse events have been described for virtually all organ systems and include, but are not limited to, colitis, pneumonitis, endocrinopathies, ocular toxicity, pancreatic toxicity, neurologic toxicity, cardiac toxicity, nephritis, myositis, and severe cutaneous adverse reactions.

Patients with a history of autoimmune disease will be excluded from this study (see Section 4.1.2).

Management guidelines for individual suspected immune-mediated adverse events are provided in Appendix 10.

5.1.1.5 Embryofetal Toxicity

Embryofetal toxicity is a potential risk with tiragolumab. Administration of tiragolumab is expected to have adverse effects on pregnancy based on the expression of TIGIT on decidual NK and $CD8^+$ T cells (Powell et al. 2017; van der Zwan et al. 2018; Vento-Tormo et al. 2018), and the expected role of these cells in the recognition and response to foreign fetal, placental, and viral antigens at the maternal-fetal interface as well as maintenance of maternal-fetal tolerance. No reproductive or teratogenicity studies in animals have been conducted with tiragolumab. There are no clinical studies of tiragolumab in pregnant women. Tiragolumab should not be administered to pregnant women.

Refer to Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of embryofetal toxicity.

5.1.2 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any

organ system and lead to hemophagocytic lymphohistiocytosis (HLH). See Appendix 10 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

Guidelines for managing patients who experience anticipated adverse events are provided in Appendix 10.

5.1.3 Risks Associated with the Combination of Tiragolumab and Atezolizumab

Based on results from clinical data with tiragolumab plus atezolizumab, there are known and potential overlapping toxicities in patients treated with tiragolumab plus atezolizumab. Because the expected pharmacologic activity of these two molecules is to increase adaptive T-cell immune responses, there is the possibility of heightened immune responses.

Refer to Section 6 of the Tiragolumab Investigator's Brochure for a list of identified risks associated with tiragolumab in combination with atezolizumab. Based on the mechanism of action of tiragolumab and atezolizumab, additional immune-mediated adverse events are potential overlapping toxicities associated with combination use of tiragolumab plus atezolizumab.

Based on clinical experience to date, it is anticipated that immune-mediated adverse events following treatment with tiragolumab and atezolizumab will be amenable to monitoring and manageable in the setting of this combination study. The extensive experience with immune checkpoint inhibitors to date has been incorporated into the design and safety management plan (see Section 5.1) in order to reduce the potential risks to participating patients. Patients with a history of autoimmune disease will be excluded from this study (see Section 4.1.2). Patients previously treated with approved or experimental CIT will also be excluded from participation in this study. [redacted]

5.1.4 Management of Adverse Events

[redacted]

5.1.4.2 Treatment Interruption

Study treatment may be temporarily suspended as appropriate for management of toxicity. On the basis of the available characterization of mechanism of action, tiragolumab may cause adverse events similar to but independent of atezolizumab, may exacerbate the frequency or severity of atezolizumab-related adverse events, or may

have non-overlapping toxicities with atezolizumab. Because these scenarios may not be distinguished from one another in the clinical setting, immune-mediated adverse events should generally be attributed to both study drugs, and dose interruptions or treatment discontinuation in response to immune-mediated adverse events should be applied to both tiragolumab/placebo and atezolizumab.



[redacted]

5.1.4.3 Management Guidelines for Tiragolumab- and Atezolizumab-Specific Adverse Events

General guidelines for management of patients who experience adverse events, including HLH and macrophage activation syndrome (MAS), are described in Appendix 10.

Guidelines for management of patients who experience adverse events associated with tiragolumab and/or atezolizumab, including immune-mediated adverse events, are provided in Appendix 10.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition; see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

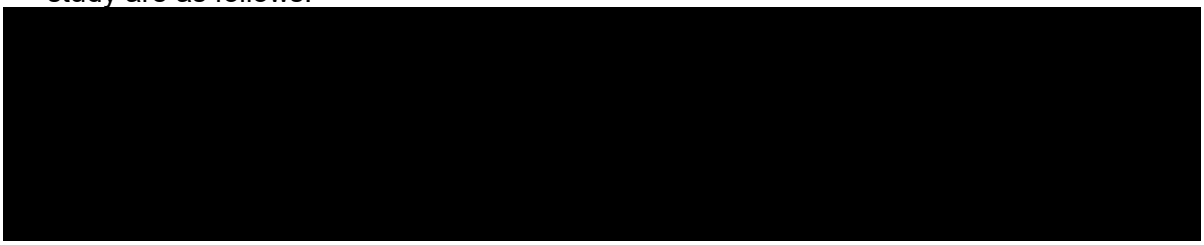
The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

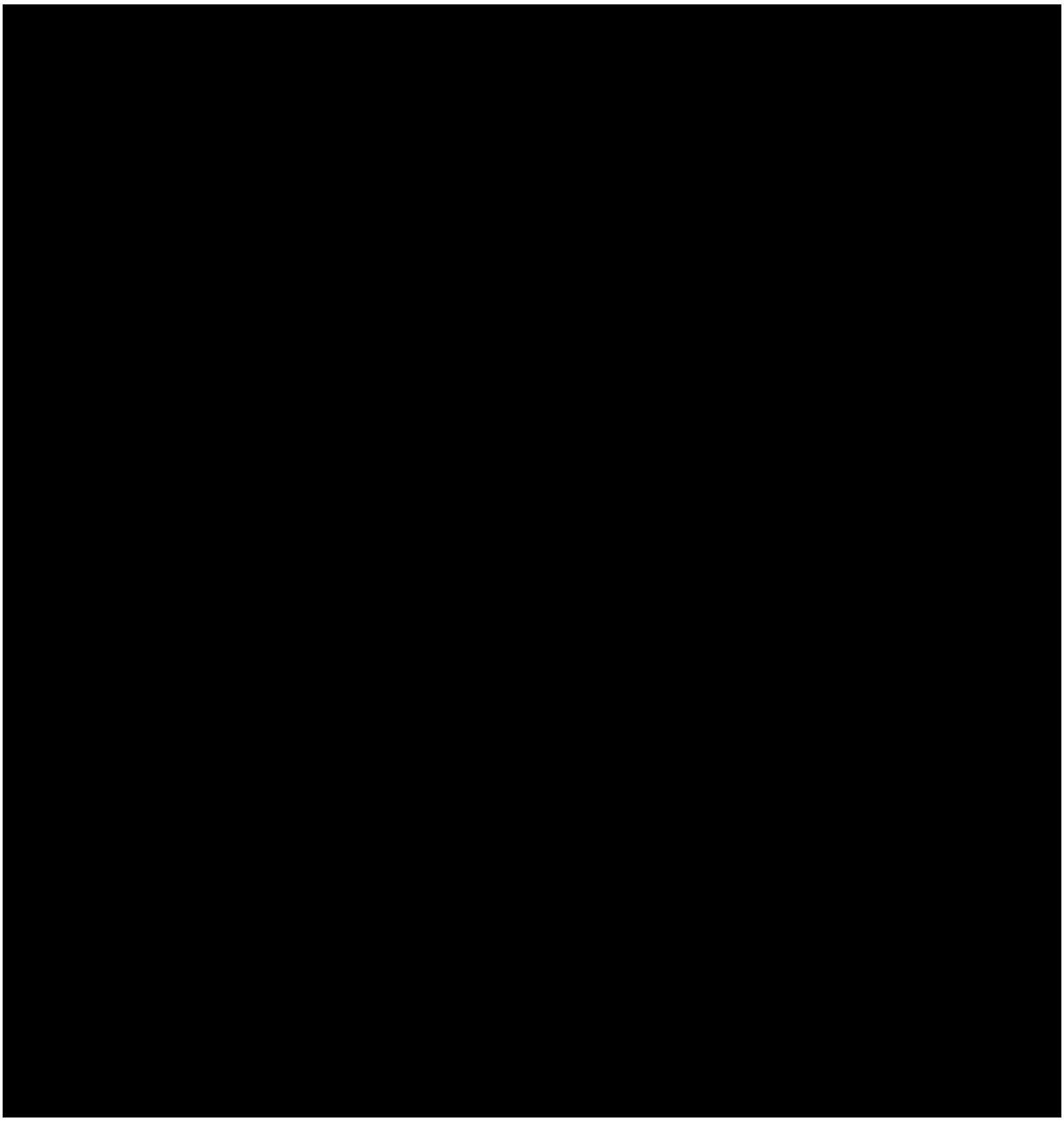
Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:





5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact.
All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study treatment, all adverse events will be reported until [redacted] days after the final dose of study treatment [redacted], and serious adverse events will continue to be reported until [redacted] days after the final dose of study treatment [redacted]. In addition, adverse events of special interest will continue to be reported until [redacted] days after the final dose of study treatment, [redacted].

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 3 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 3 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

The American Society for Transplantation and Cellular Therapy (ASTCT) CRS consensus grading scale (see Table 4) should be used in addition to NCI CTCAE when reporting severity of CRS.

Table 4 ASTCT CRS Consensus Grading

Grade	Symptoms
1	• Fever [a] with or without constitutional symptoms • No hypotension • No hypoxia
2	• Fever [a] combined with at least one of the following: – Hypotension not requiring vasopressors – Hypoxia requiring low-flow oxygen [b] by nasal cannula or blow-by
3	• Fever [a] combined with at least one of the following: – Hypotension requiring one vasopressor with or without vasopressin – Hypoxia requiring high-flow oxygen [b] by nasal cannula, face mask, non-rebreather mask, or Venturi mask
4	• Fever [a] combined with at least one of the following: – Hypotension requiring multiple vasopressors (excluding vasopressin) – Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)
5	• Death due to CRS in which another cause is not the principal factor leading to this outcome

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome.

[a] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who develop CRS and then receive antipyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining CRS severity (grade). In this case, the CRS grade is driven by the presence of hypotension and/or hypoxia.

[b] Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 5):

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (as applicable)
- Known association of the event with study treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event

- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

Table 5 Causal Attribution Guidance

Is the adverse event suspected to be caused by study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of study treatment, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to study treatment; and/or the adverse event abates or resolves upon discontinuation of study treatment or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of study treatment (e.g., cancer diagnosed 2 days after first dose of study treatment).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions and Cytokine-Release Syndrome

There may be significant overlap in signs and symptoms of IRRs and CRS. While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, HLH, tumor lysis syndrome, early disease progression, or other manifestations of systemic inflammation.

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., "infusion-related reaction" or "cytokine-release syndrome") on the Adverse Event eCRF. Avoid ambiguous terms such as "systemic reaction." Cases of late-onset CRS should be reported as "cytokine-release syndrome" on the Adverse Event eCRF. Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF or Cytokine-Release Syndrome eCRF, as appropriate.

If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF or Cytokine-Release Syndrome eCRF.

NCI CTCAE v5.0 and the ASTCT CRS consensus grading scale (see Section 5.3.3) should be used when reporting severity of CRS on the Adverse Event eCRF.
NCI CTCAE v5.0 should be used when reporting severity of organ toxicities associated with CRS on the dedicated Cytokine-Release Syndrome eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

Guidelines for medical management of IRR and CRS are provided in Appendix 10 (Table 7 and Table 8, respectively).

5.3.5.2 Diagnosis Versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

    Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range

(e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of

the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of NSCLC should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An independent monitoring committee will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of NSCLC

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is because of disease progression, it should be

reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Cases of Tiragolumab/Placebo or Atezolizumab Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the

event; see Section 5.4.2). For tiragolumab/placebo and atezolizumab, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with tiragolumab/placebo and atezolizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO-CTCAE or other PRO data by the Sponsor. In addition, the Sponsor will make no attempt to reconcile patient reports of study treatment–related symptoms (using the PRO-CTCAE) with investigator reports of adverse events. Sites are not expected to review the PRO-CTCAE or other PRO data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report

such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

To ensure the safety of study patients, access to Medical Monitors is available 24 hours per day, 7 days per week. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center Help Desk, will be distributed to investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur Prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Adverse Event/ Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur After Study Treatment Initiation

After initiation of study treatment, serious adverse events will be reported until [redacted] days after the final dose of study treatment [redacted]. In addition, adverse events of special interest will be reported until [redacted] days after the final dose of study treatment, [redacted]. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/ Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur after the reporting period are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 90 days after the final dose of tiragolumab/placebo or within 5 months after the final dose of atezolizumab. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.
Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 90 days after the final dose of tiragolumab/placebo. The investigator should report the

pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all

serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for serious adverse events (defined as [redacted] days after the final dose of study treatment [redacted], whichever occurs first) and adverse events of special interest (defined as [redacted] days after the final dose of study treatment, [redacted], all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authorities (which

includes the use of applicable systems, such as EudraVigilance), IRBs, ECs, and investigators.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
Tiragolumab	Tiragolumab Investigator's Brochure
Atezolizumab	Atezolizumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An iDMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a Phase III, global, multicenter, randomized, double-blinded, placebo-controlled study, designed to evaluate the efficacy and safety of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated locally advanced unresectable or metastatic PD-L1–selected NSCLC.

[redacted]

Efficacy analyses will be performed with patients grouped according to the treatment assigned at randomization, regardless of whether they receive any assigned study treatment.

Safety analyses will be conducted in all randomized patients who receive at least one dose of tiragolumab/placebo or atezolizumab. Safety analyses will be performed by treatment arm and will be based on actual treatment received. Specifically, a patient will be included in the tiragolumab plus atezolizumab arm in the safety analyses if the patient receives any amount of tiragolumab, regardless of the initial treatment assignment at randomization.

Hypothesis tests will be two sided unless otherwise indicated. Details of the analyses will be provided in the Statistical Analysis Plan (SAP).

6.1 DETERMINATION OF SAMPLE SIZE

The co-primary endpoint of PFS and OS will be analyzed in the PAS (defined as the randomized patients with high tumor PD-L1 expression [redacted] This study will enroll approximately 500 patients in the PAS.

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

6.1.2 Co-Primary Endpoint: Progression-Free Survival in the Primary Analysis Set

The primary analysis of the co-primary endpoint of PFS in the PAS will occur when approximately [redacted] PFS events ([redacted] patients) or approximately [redacted] OS events ([redacted] patients) have been observed in this analysis set, whichever comes later (see Section 6.1.3). The [redacted] PFS events provides a [redacted] power to detect a target HR of [redacted] or PFS at a two-sided significance level of [redacted] based on the following assumptions:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

6.1.3 Co-Primary Endpoint: Overall Survival in the Primary Analysis Set

The final analysis of the co-primary endpoint of OS will occur when approximately [redacted] deaths ([redacted]; see Section 6.4.1) have been observed in the PAS. This provides an [redacted] power to detect a target HR of [redacted] for OS in the PAS at a two-sided significance level of [redacted] based on the following assumptions:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.1.4 Secondary Endpoint: Progression-Free Survival and Overall Survival in the Secondary Analysis Set

If the difference in the OS in the PAS is statistically significant at an α of [redacted] or [redacted] that same α will become the [redacted] for the SAS, with α allocated to PFS and OS in this analysis set at the same [redacted] ratio. PFS and OS in the SAS will be analyzed at the same time as for the PAS.

6.2 SUMMARIES OF CONDUCT OF STUDY

Study enrollment, study drug administration, reasons for study drug discontinuation, and reasons for discontinuation from the study will be summarized by treatment arm.
Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic (including age, sex, race/ethnicity) and baseline disease characteristics (e.g., ECOG Performance Status) will be summarized overall and by treatment arm.

Descriptive statistics (mean, median, standard deviation, and range) will be presented for continuous data, and frequencies and percentages will be presented for categorical data, as appropriate.

Baseline measurements are the last available data obtained prior to the patient receiving the first dose of any component of study treatment.

6.4 EFFICACY ANALYSES

The efficacy analyses will be performed in the PAS and/or SAS unless otherwise specified. Patients are grouped according to their assigned treatment for efficacy analyses.

6.4.1 Co-Primary Efficacy Endpoints

The co-primary efficacy endpoints are PFS, as assessed by the investigator according to RECIST v1.1, and OS in the PAS.

Progression-free survival is defined as the time between the date of randomization and the date of first documented disease progression as assessed by investigators according to RECIST v1.1, or death, whichever occurs first. Patients who have not experienced disease progression and have not died at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of randomization.

Overall survival is defined as the time between the date of randomization and death from any cause.

Data for patients who are not reported as having died at the date of analysis will be censored at the date when they were last known to be alive. Data for patients who do not have post-baseline information will be censored at the date of randomization.

Progression-free survival and OS will be compared between treatment arms with use of the stratified log-rank test. The HR for PFS and OS will be estimated using a stratified Cox proportional hazards model. The 95% CI for the HR will be provided.
The stratification factors will be the same as the randomization stratification factors: ECOG Performance Status (0 vs. 1), tumor histology (non-squamous vs. squamous), and geographic region of the enrolling site (Asia vs. non-Asia). Stratification factor(s) may be removed from the stratified analyses if there is risk of over stratification. Analyses based on stratification factors recorded on the eCRF will also be provided if considerable discrepancy is observed between IxRS records and eCRFs. Results from an unstratified analysis will also be provided.

Kaplan-Meier methodology will be used to estimate the median PFS and median OS for each treatment arm, and Kaplan-Meier curves will be constructed to provide a visual description of the difference between treatment arms. The Brookmeyer-Crowley

methodology will be used to construct the 95% CI for the median PFS and median OS for each treatment arm (Brookmeyer and Crowley 1982).

The timing of the final PFS analysis is described in Section 6.1.2 and the analyses timing for OS is described in Section 6.1.3. [redacted]

6.4.2 Secondary Efficacy Endpoints

6.4.2.1 Investigator-Assessed Progression-Free Survival and Overall Survival in the Secondary Analysis Set

Investigator-assessed PFS and OS in the SAS will be analyzed at the same time as for the PAS using the same methods described for the PFS and OS analyses in the PAS (see Section 6.4.1). [redacted]

6.4.2.2 Confirmed Objective Response Rate

A confirmed objective response is defined as either a CR or PR on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1. Patients not meeting these criteria, including patients without any post-baseline tumor assessment, will be considered non-responders.

Confirmed ORR is defined as the proportion of patients who achieve a confirmed objective response. Patients must have measurable disease at baseline to be included in the analysis. The confirmed ORR will be compared between the two treatment arms using the stratified Mantel-Haenszel test. The stratification factors of this analysis will be the same as those described in Section 6.4.1. The 95% CI for the difference in confirmed ORRs between the treatment arms will be computed using the Newcombe method. The 95% CI of the confirmed ORR will be calculated for each treatment arm using the Wilson score method.

6.4.2.3 Duration of Response

Duration of response will be assessed in patients who achieved a confirmed objective response, as determined by the investigator according to RECIST v1.1. Duration of response is defined as the time interval from the date of the first occurrence of a confirmed objective response until the first date of progressive disease as determined by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first. Patients who have not progressed and who have not died at the time of analysis will be censored at the time of the last tumor assessment date. Duration of response will

be based on a non-randomized subset of patients (specifically, patients who achieve a confirmed objective response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes.

6.4.2.4 Progression-Free Survival Rate at Landmark Timepoints

The PFS rate at 6 months and 12 months will be estimated using Kaplan-Meier methodology for each treatment arm and the 95% CIs calculated using the standard error derived from Greenwood's formula. The 95% CI for the difference in PFS rates between the two treatment arms will be estimated using the normal approximation method.

6.4.2.5 Overall Survival Rate at Landmark Timepoints

The OS rate at 12 months and 24 months will be estimated using Kaplan-Meier methodology for each treatment arm and the 95% CIs calculated using the standard error derived from Greenwood's formula. The 95% CI for the difference in OS rates between the two treatment arms will be estimated using the normal approximation method.

6.4.2.6 Patient-Reported Outcomes

Time to confirmed deterioration for physical functioning and GHS/QoL using the EORTC QLQ-C30 is defined as the time from the date of randomization until the first confirmed clinically meaningful deterioration.

Confirmed clinically meaningful deterioration for physical functioning and GHS/QoL is defined as a clinically meaningful decrease from baseline in physical functioning or GHS/QoL score that must be held for at least two consecutive assessments or an initial clinically meaningful decrease above baseline followed by death from any cause within 6 weeks.

A score change of ≥ 10 points in GHS/QoL and functional subscale score is perceived by patients as clinically meaningful (Osoba et al. 1998).

For TTCD, data for patients will be censored at the last time when they completed an assessment if they have not experienced a confirmed clinically meaningful deterioration at the clinical cutoff date. If no baseline or post-baseline assessment is performed, patients will be censored at the randomization date. TTCD using the EORTC scale will be analyzed using the same methods as for PFS. Additional details regarding the TTCD analysis for the EORTC measures will be described in the SAP.

Summary statistics (mean, SD, median, 25th and 75th percentiles, and range) and the mean change from baseline of linearly transformed scores will be reported for all of the items and subscales of the EORTC QLQ-C30 and EORTC IL46, an item for troubled by side effects questionnaires according to the EORTC scoring manual guidelines.



Completion and compliance rates will be summarized at each timepoint by treatment arm.

6.5 SAFETY ANALYSES

Safety analyses will be conducted in patients who receive at least one dose of tiragolumab/placebo or atezolizumab.

Safety analyses will be performed by treatment arm and will be based on actual treatment received. Specifically, a patient will be included in the tiragolumab plus atezolizumab arm in the safety analyses if the patient receives any amount of tiragolumab, regardless of the initial treatment assignment at randomization.

Safety endpoints will include the incidence and severity of adverse events, with severity determined according to the NCI CTCAE v5.0 (and also according to the ASTCT consensus grading scale for CRS), including serious adverse events and adverse events of special interest, and clinical laboratory results following the administration of study drugs. Drug exposure will be summarized, including duration, dosage, and dose intensity. Verbatim description of adverse events will be mapped to the MedDRA thesaurus terms and graded according to the NCI CTCAE v5.0 (and also according to the ASTCT consensus grading scale for CRS). All adverse events will be summarized by treatment arm and NCI CTCAE grade and (and also ASTCT consensus grade for CRS). In addition, serious adverse events and adverse events leading to study treatment discontinuation or interruption will be summarized accordingly.
Multiple occurrences of the same event will be counted once at the maximum severity.
Laboratory data with values outside of the normal ranges will be identified.
Additionally, selected laboratory data, including ADA results, will be summarized by treatment arm. Deaths and causes of deaths will be summarized.

6.6 PHARMACOKINETIC ANALYSES

Pharmacokinetic samples will be collected in this study as outlined in Appendix 2. Tiragolumab and atezolizumab serum concentration data (minimum concentration observed [C_{min}] and maximum concentration observed [C_{max}]) will be tabulated and summarized. Descriptive statistics will include means, medians, ranges and standard deviations, as appropriate.

Additional PK analyses will be conducted, as appropriate, based on the availability of data.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include patients with any ADA assessments, with patients grouped according to treatment received.

The number and proportion of treatment-emergent ADA-positive patients and ADA-negative patients during both the treatment and follow-up periods will be summarized by treatment arm.

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

6.10.4 Safety Monitoring

The iDMC will convene to review [redacted] safety analysis results. See Section 3.1.2 for additional details regarding the iDMC.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

Electronic Case Report Forms and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Patient-reported outcome data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

Electronic Case Report Forms are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. Electronic Case Report Forms will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. Electronic Case Report Forms should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered on the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly on the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, paper PRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor.
Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the E.U. or European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form will be provided to each site.
If applicable, it will be provided in a certified translation of the local language.

The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Informed Consent Form will also contain a separate signature page for patients who meet all of the criteria specified in Section 3.1.1 and who decide to continue study treatment beyond radiographic disease progression per RECIST v1.1. This separate consent is to be signed after initial radiographic disease progression has occurred and patients have discussed other available treatment options and the potential risks of continuing study treatment.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC

policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data, and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 150 sites globally will participate to randomize approximately 560 patients. Screening, enrollment, and blinded treatment assignment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker analyses, and PK analyses), as specified in Section 4.5.7. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will monitor and evaluate patient safety throughout the study as specified in Section 3.1.2. Tumor response and progression will be evaluated by the investigator. All primary imaging data used for tumor assessments will be collected by the Sponsor and a centralized, blinded independent review by an IRF may be conducted.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

Assessment	Screening [a] Days –28 to –1	All Treatment Cycles [b] Every 21 Days (±3 Days)	Treatment Discontinuation Visit [c] ≤30 Days after Final Dose	Survival Follow-Up [d] Approx. every 3 Months after Disease Progression or Loss of Clinical Benefit
Signed ICF(s) [e] • Prescreening ICF for central PD-L1 testing • Main ICF for study participation	x			
[redacted]	x			
Demographics (sex, age, and self-reported race/ethnicity)	x			
Medical history, including NSCLC history and baseline conditions [g]	x			
EGFR and *ALK* mutational status [h]	x			
Vital signs [i]	x	x	x	
Weight	x			
Height	x			
Complete physical examination [j]	x			
Limited physical examination [j]		x [k]	x	
ECOG Performance Status	x	x [k]	x	
ECG [l]	x			
Hematology [m]	x [n]	x [k]	x	
Chemistry profile (serum or plasma) [o]	x [n]	x [k]	x	

Appendix 1: Schedule of Activities (cont.)

Assessment	Screening [a]	All Treatment Cycles [b]	Treatment Discontinuation Visit [c]	Survival Follow-Up [d] Approx. every 3 Months after Disease Progression or Loss of Clinical Benefit
	Days –28 to –1	Every 21 Days (±3 Days)	≤30 Days after Final Dose	
Coagulation test: INR or aPTT	x [n]		x	
Pregnancy test (for women of childbearing potential only) [p]	x	x	x	
TSH, free T3, and free T4 [q]	x	x [q]	x	
[redacted]	x			
Urinalysis [s]	x			
CT scan with contrast (or MRI scan) of the head [t]	x	x [w]		
Atezolizumab IV infusion [u]		x		
Tiragolumab/placebo IV infusion [u]		x		
Cancer-related procedures (medical, surgical, and radiation)		x	x	x
Concomitant medications [v]	x	x	x	
Tumor assessment [w, x]	x	x [x]		
Informed consent to continue study treatment beyond radiographic disease progression per RECIST v1.1		At time of initial radiographic progression		
PROs (EORTC QLQ-C30, EORTC IL46, [redacted] and EQ-5D-5L) [y]		x	x	x
Adverse events [z]		x	x	x

Appendix 1: Schedule of Activities (cont.)

Assessment	Screening [a]	All Treatment Cycles [b]	Treatment Discontinuation Visit [c]	Survival Follow-Up [d] Approx. every 3 Months after Disease Progression or Loss of Clinical Benefit
	Days –28 to –1	Every 21 Days (±3 Days)	≤30 Days after Final Dose	
Serum sample for ADA and PK assessment (central laboratory) [aa]	Refer to Appendix 2 for the ADA and PK sampling schedule.			
Blood samples for biomarkers (central laboratory) [aa]	Refer to Appendix 2 for the biomarker sampling schedule.			
[redacted]		x	x	
Survival and anti-cancer therapy follow-up [d]				x

ADA=anti-drug antibody; *ALK*=anaplastic lymphoma kinase; CT=computed tomography; [redacted] EBUS=endobronchial ultrasound; EBUS TBNA=endobronchial ultrasound-guided transbronchial needle aspirations; [redacted] ECOG=Eastern Cooperative Oncology Group; *EGFR*=epidermal growth factor receptor; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire–Core 30; EUS=endoscopic ultrasound; EUS-FNA=endoscopic ultrasound-guided fine-needle aspiration; [redacted] ICF Informed Consent Form; [redacted] LDH lactate dehydrogenase; MRI magnetic resonance imaging; NSCLC=non–small cell lung cancer; PCR=polymerase chain reaction; PD–L1=programmed death–ligand 1; PET=positron emission tomography; PK=pharmacokinetic; PRO=patient-reported outcome; [redacted] QLQ-C30=Quality of Life Questionnaire Core 30; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; T3=free triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; VCA=viral capsid antigen.

Notes: All treatment visits must occur ±3 days from the scheduled date unless otherwise noted. All assessments will be performed on the day of the specified visit unless a time window is specified. [redacted]

[a] Screening tests and evaluations will be performed within 28 days prior to Day 1 of Cycle 1. [redacted]

[c] Patients will be asked to return to the clinic not more than 30 days after the final dose of study treatment for a treatment discontinuation visit.

[d] After radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for patients who continue study treatment after disease progression per RECIST v1.1) and study treatment has been discontinued, survival follow-up information will be collected by telephone, patient medical records, and/or clinic visits approximately every 3 months (±30 days) or more frequently until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first. All patients will be periodically contacted for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from follow-up (this request must be documented in the source documents and signed by the investigator). If the patient withdraws from the study, study staff may use a public information source (e.g., county records) when permissible to obtain information about survival status.

[e] Written informed consent is required for performing any study-specific tests or procedures. Signing of the ICFs can occur outside the 28-day screening period. Patients have the option to sign the Prescreening ICF to consent to PD-L1 tissue testing (and central evaluation of *EGFR* and/or *ALK* status for patients with non-squamous NSCLC if requested) during prescreening, prior to signing the main ICF for all screening procedures and study participation.

[f] [redacted]

[g] Medical history, including clinically significant diseases, surgeries, reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. Cancer history includes stage, date of diagnosis, prior cancer therapies and procedures, *EGFR* and *ALK* mutational status, and status of other mutations if known.

[h] Patients with non-squamous NSCLC who have unknown *EGFR* or *ALK* status will be required to be tested at prescreening or screening. Patients with squamous NSCLC who have an unknown *EGFR* or *ALK* status are eligible and will not be required to be tested at prescreening or screening. *EGFR* and/or *ALK* status may be assessed locally or at a central laboratory. *EGFR* status assessed locally must be performed on tissue or cytology using a validated health authority approved test that detects mutations in exons 18–21. If samples are submitted for central *EGFR* and/or *ALK* testing, an [redacted] (see Sections 4.1.2 and 4.5.7).

[i] Vital signs include pulse rate, respiratory rate, blood pressure, and temperature. Vital signs should be recorded as described in Section 4.5.4.

[j] Complete and limited physical examinations are defined in Section 4.5.3.

[k] ECOG Performance Status, physical examination, and local laboratory assessments may be obtained ≤ 96 hours before Day 1 of each cycle.

[l] An ECG is required at screening and as clinically indicated during the study. [redacted]

[m] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with automated differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils), and platelet count.

[n] At screening, patients must have adequate hematologic and end-organ function defined by laboratory results obtained within 14 days prior to initiation of study treatment (Day 1 of Cycle 1), as described in Section 4.1.1.

[o] Chemistry panel (serum or plasma) includes BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the region), calcium, phosphate, glucose, total bilirubin, ALT, AST, ALP, LDH, total protein, and albumin.

[p] All women of childbearing potential (including those who have had a tubal ligation) must have a serum pregnancy test performed at screening and documented as negative within 14 days prior to initiation of study treatment. During the study, urine pregnancy tests will be performed on Day 1 of every cycle. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[q] TSH, free T3 (or total T3 at sites where free T3 is not performed), and free T4 will be collected at screening, on Day 1 of Cycle 1, and every fourth cycle thereafter (e.g., Cycles 1, 5, 9, 13, and so forth).

[r] [redacted]

[s] Urinalysis (dipstick permitted; specific gravity, pH, glucose, protein, ketones, and blood). Urinalysis is required at screening and as clinically indicated during the study.

[t] A CT scan with contrast or MRI scan with contrast (if CT contrast is contraindicated) of the head must be performed at screening to evaluate CNS metastasis in all patients. If a CT scan with contrast is performed and the presence of brain metastases is considered equivocal, an MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline. Patients with active or untreated CNS metastases are not eligible for the study (see Section 4.1.2).

[u] Atezolizumab will be administered prior to tiragolumab/placebo. Patients will receive atezolizumab by continuous IV infusion every 21 days on Day 1 of each 21-day cycle as indicated. For atezolizumab, the initial dose will be delivered over [redacted] minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. Following atezolizumab, patients will receive tiragolumab or placebo by continuous IV infusion every 21 days on Day 1 of each 21-day cycle as indicated. For tiragolumab or placebo, the initial dose will be delivered over [redacted] minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over [redacted] minutes. Dosing of both study drugs will occur only if the clinical assessment and local laboratory test results are acceptable. If a tumor assessment was performed, results must be reviewed by the investigator before dosing of study treatment.

[v] Concomitant medications include any prescription medications, over-the-counter medications, vaccines, herbal or homeopathic remedies, or nutritional supplements. Any medications the patient has used within the 7 days prior to the initiation of study treatment should be documented. At subsequent visits, changes to current medications or medications used since the last documentation will be recorded.

[w] Tumor assessments performed as standard-of-care prior to obtaining informed consent and within 28 days prior to Cycle 1 Day 1 may be used rather than repeating tests. All known sites of disease, including measurable and/or non-measurable disease, must be documented at screening and re-assessed at each subsequent tumor evaluation. Screening and subsequent tumor assessments must include CT scans (with IV contrast unless contraindicated and oral contrast as appropriate per institutional standards) of the chest and abdomen. A CT scan with contrast of the pelvis is required at screening and as clinically indicated or as per local standard of care at subsequent response evaluations. MRI scans with contrast of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest may be used in patients for whom CT scans with IV contrast are contraindicated (i.e., patients with iodine-based contrast allergy or impaired renal clearance). A CT (with contrast if not contraindicated) or MRI scan of the head must be performed at screening to evaluate CNS metastasis in all patients. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan. [redacted]

[x] Patients will undergo tumor assessments at baseline and at every 6 weeks (± 7 days) for 48 weeks following Day 1 of Cycle 1 regardless of treatment delays. After the completion of the Week 48 tumor assessment, tumor assessments will be required every 9 weeks (± 7 days) regardless of treatment delays, until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for patients who continue study treatment after disease progression per RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. At the investigator's discretion, scans may be performed at any time if progressive disease or loss of clinical benefit is suspected. The investigator's assessment of overall tumor response at all timepoints should only be based on RECIST v1.1 (see Appendix 4). Assessments should be performed by the same evaluator if possible to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle. Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments at the frequency described above until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by Sponsor, whichever occurs first. In the absence of radiographic disease progression per RECIST v1.1, tumor assessments should continue regardless of whether a patient starts a new anti-cancer therapy.

[y] [redacted]

[z] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until [redacted] days after the final dose of study treatment [redacted] and serious adverse events will continue to be reported until [redacted] days after the final dose of study treatment [redacted] In addition, adverse events of special interest will continue to be reported until [redacted] days after the final dose of study treatment, [redacted]. After this period, all deaths, regardless of cause, should be reported. In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the adverse event should be reported. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or protocol-related procedures until a final outcome can be reported.

[aa] Refer to the table in Appendix 2 for details of the PK, immunogenicity, and biomarker collection schedule. Blood samples should be processed to obtain serum and plasma.

[bb] For patients who agree to optional biopsies, biopsy samples may be collected at any time if clinically feasible at the investigator's discretion, but preferably at the time of radiographic response or radiographic progression. Recommended samples for optional tumor biopsies include core needle biopsies for deep tumor tissue or organs, or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions at the investigator's discretion. Patients who agree to collection of optional biopsies must sign the Optional Biopsy Sample ICF.

Appendix 2
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

[redacted]

a [redacted]

b [redacted]

c [redacted]

Appendix 3
Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active; able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework or office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about $>$50% of waking hours.
3	Capable of only limited self-care; confined to a bed or chair $>$50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix 4
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1; Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

[1] For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 mm but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99 m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of

non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be used for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm

but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non-lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is <5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non-lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in short axis.
Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis <10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).

- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm

there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table A4-1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table A4-1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not all evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective

progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table A4-1.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

Appendix 5
European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30) and EORTC Item List 46 (EORTC IL46)



EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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ENGLISH



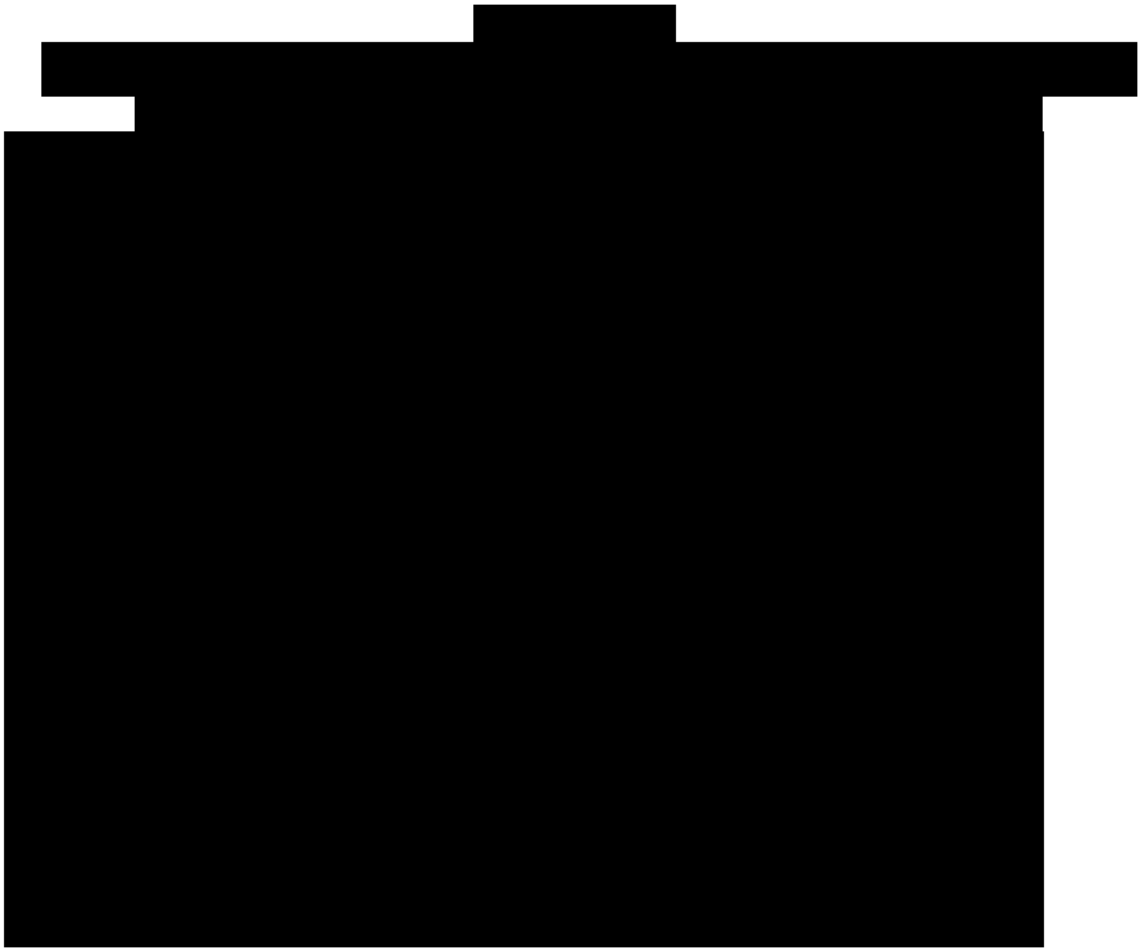
EORTC IL46

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
1. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4

SPECIMEN

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Appendix 7
EuroQol 5-Dimension Questionnaire (EQ-5D-5L)



Health Questionnaire

English version for the USA

USA (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

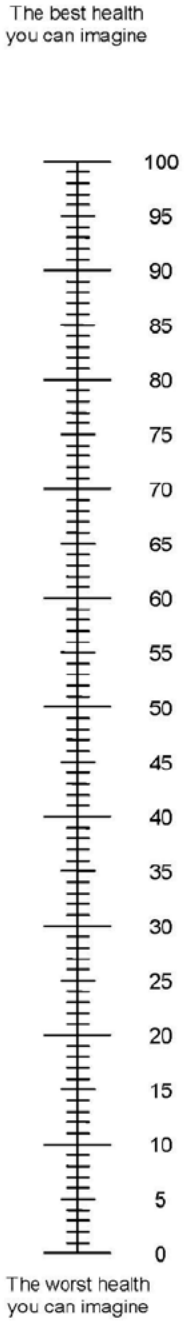
I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

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- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

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Appendix 8
Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab and tiragolumab for patients who have previously experienced a severe or life-threatening skin adverse reaction or pericardial disorder while receiving another immunostimulatory anti-cancer agent. The Medical Monitor is available to advise on any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies



Appendix 9
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.

Appendix 10
Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events Associated with Tiragolumab and/or Atezolizumab

Toxicities associated or possibly associated with atezolizumab and/or tiragolumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology when clinically indicated.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of tiragolumab and/or atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related.

The following are general recommendations for management of any other adverse events that may occur and are not specifically listed in subsequent subsections.



[redacted]

TREATMENT INTERRUPTION

Atezolizumab and tiragolumab/placebo treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment.

[redacted]

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Patients will be assessed for pulmonary signs and symptoms throughout the study.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. The COVID-19 evaluation should be performed per institutional guidelines where relevant. Management guidelines for pulmonary events are provided in Table A10-1.

Table A10-1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]

Table A10-1 Management Guidelines for Pulmonary Events, Including Pneumonitis (cont.)

Event	• Management
[redacted]	[redacted]

HEPATIC EVENTS

Patients eligible for study treatment must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table A10-2.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug(s).

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table A10-2 Management Guidelines for Hepatic Events

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted].

a [redacted]

Table A10-2 Management Guidelines for Hepatic Events (cont.)

b [redacted]

c [redacted]

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Table A10-3.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Table A10-3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]

Table A10-3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis; cont.)

Event	Management
	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table A10-3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis; cont.)

GI = gastrointestinal.

a [redacted]

b [redacted]

c [redacted]

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table A10-4.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table A10-4 Management Guidelines for Endocrine Events

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table A10-4 Management Guidelines for Endocrine Events (cont.)

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table A10-4 Management Guidelines for Endocrine Events (cont.)

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

a [redacted]

b [redacted]

Table A10-4 Management Guidelines for Endocrine Events (cont.)

[redacted]

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

a [redacted]

b

c

IMMUNE-MEDIATED CARDIAC EVENTS

[redacted] Management guidelines for cardiac events are provided in Table A10-6.

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., *troponin,* B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis or associated with pericarditis (see section on *immune-mediated* pericardial disorders below) and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

[redacted]

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A10-6.

IMMUNE-MEDIATED PERICARDIAL DISORDERS

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on *immune-mediated* myocarditis above).

[redacted]

Event	Management
[redacted]	[redacted]

[redacted]

Event	Management
	[redacted]

[redacted]

INFUSION-RELATED REACTIONS

[redacted]

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with tiragolumab and atezolizumab. [redacted]

Guidelines for the medical management of IRRs during Cycle 1 are provided in Table A10-7. [redacted]

Table A10-7 Management Guidelines for Infusion-Related Reactions

Event	Management
[redacted]	[redacted]

Table A10-7 Management Guidelines for Infusion-Related Reactions (cont.)

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

a [redacted]

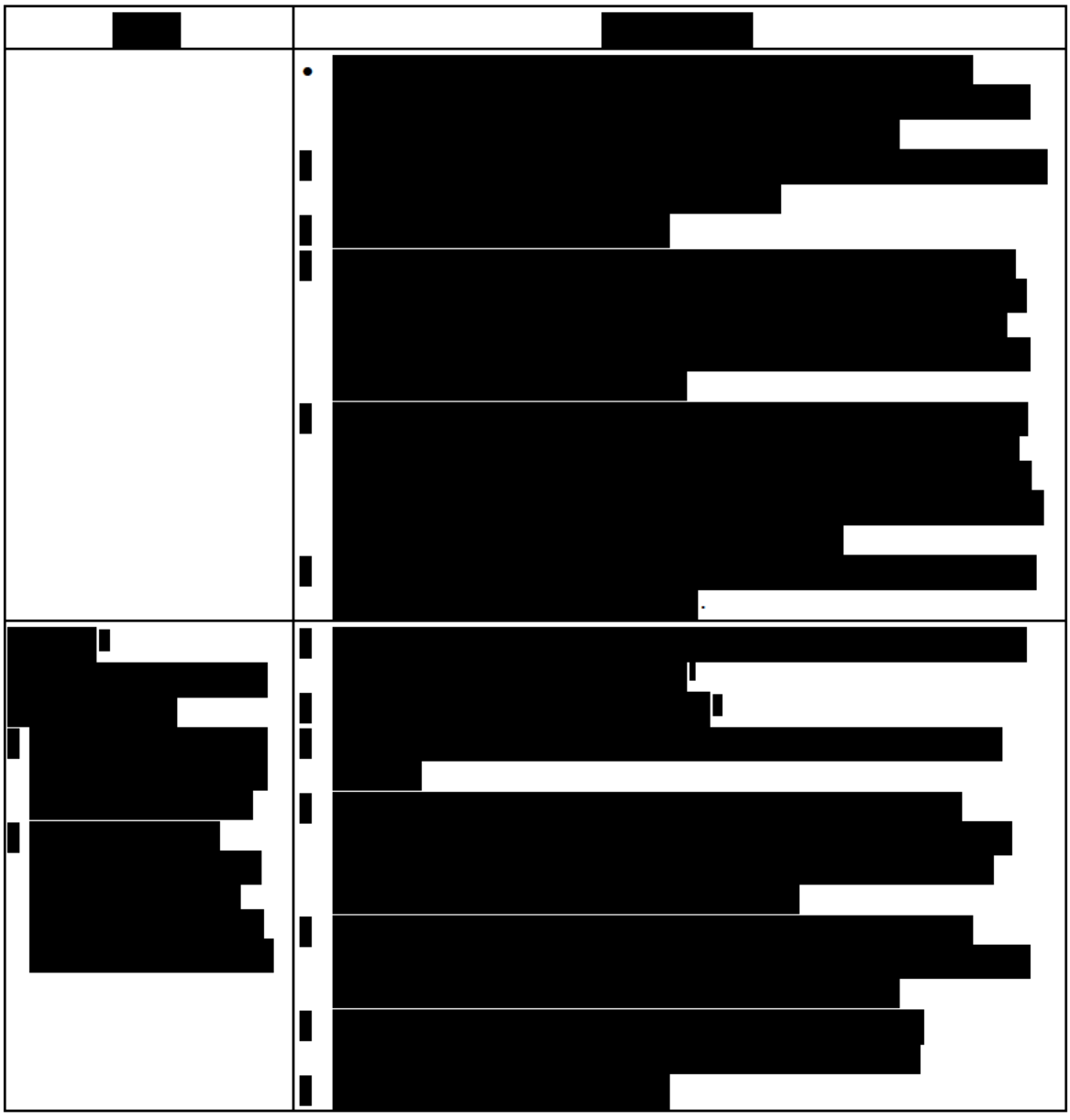
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

PANCREATIC EVENTS

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table A10-9.

Table A10-9 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
[redacted]	[redacted]

Table A10-9 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]

Table A10-9 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
[redacted]	[redacted]

GI = gastrointestinal.

a [redacted]

b [redacted]

c [redacted]

DERMATOLOGIC EVENTS

The majority of cases of rash reported with the use of atezolizumab and/or tiragolumab were mild in severity and self-limiting, with or without pruritus. [redacted] Management guidelines for dermatologic events are provided in Table A10-10.

Table A10-10 Management Guidelines for Dermatologic Events

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table A10-10 Management Guidelines for Dermatologic Events (cont.)



NEUROLOGIC DISORDERS

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. *Myasthenia may be associated with myositis (see section on immune-mediated myositis) and patients should be managed accordingly.* Management guidelines for neurologic disorders are provided in Table A10-11 with specific guidelines for myelitis provided in Table A10-12.

Table A10-11 Management Guidelines for Neurologic Disorders

Event	Management

Table A10-11 Management Guidelines for Neurologic Disorders (cont.)

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table A10-11 Management Guidelines for Neurologic Disorders (cont.)

[redacted]

a [redacted]

b

c

[redacted]

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

[redacted]

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A10-13.

Table A10-13 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
[redacted]	[redacted]

RENAL EVENTS

Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A10-14.

Table A10-14 Management Guidelines for Renal Events

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

a [redacted]

b

c

IMMUNE-MEDIATED MYOSITIS

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. [redacted]

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A10-15.

Table A10-15 Management Guidelines for Immune-Mediated Myositis

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table A10-15 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
[redacted]	[redacted]

[redacted]

a [redacted]

b [redacted]

c [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

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Appendix 11
Investigational Medicinal Product and *Auxiliary* Medicinal Product Designations (for Use in European Economic Area)

Table A11-1 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for European Economic Area

Product Name	IMP/AxMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Tiragolumab (RO7092284)	IMP (test product)	Unauthorized	Not applicable
Atezolizumab (RO5541267)	IMP (test product) [a]	Authorized	No [b]
Tiragolumab placebo	IMP (placebo)	Unauthorized	Not applicable

1 L = first-line; AxMP = auxiliary medicinal product; EEA = European Economic Area; IMP = investigational medicinal product.

[a] Atezolizumab is considered to be an IMP test product as well as an IMP comparator.

[b] Atezolizumab is approved for the treatment of PD-L1 high 1 L non-small cell lung cancer but not in combination with tiragolumab.

Signature Page for Protocol - GO41717 - TIRAGOLUMAB - v7 - Global/Core - Publish
System identifier: RIM-CLIN-511577

Approval Task	[redacted] Company Signatory 14-Nov-2023 05:59:46 GMT+0000